Neurology

OFFICIAL JOURNAL OF
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FEBRUARY--1959
Volume 9 : Number 2

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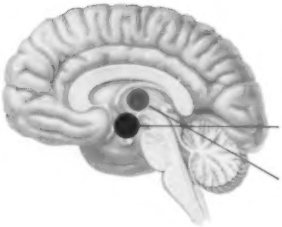

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1. Rinaldi, F., and Himwich, M.E.: Dis. Nerv. System *16*:133-141 (May) 1955.
2. Berger, F.M.: J. Pharmacol. & Exper. Therap. *112*:413-423 (Dec.) 1954.
3. Ehrmantraut, W., et al.: Presented as a Scientific Exhibit, District of Columbia Medical Society Convention, Nov. 24-26, 1958.
4. Parks, R.V.: Internat. Rec. M. *171*:678-683 (Nov.) 1958.
5. Case reports on file at Wyeth Laboratories.

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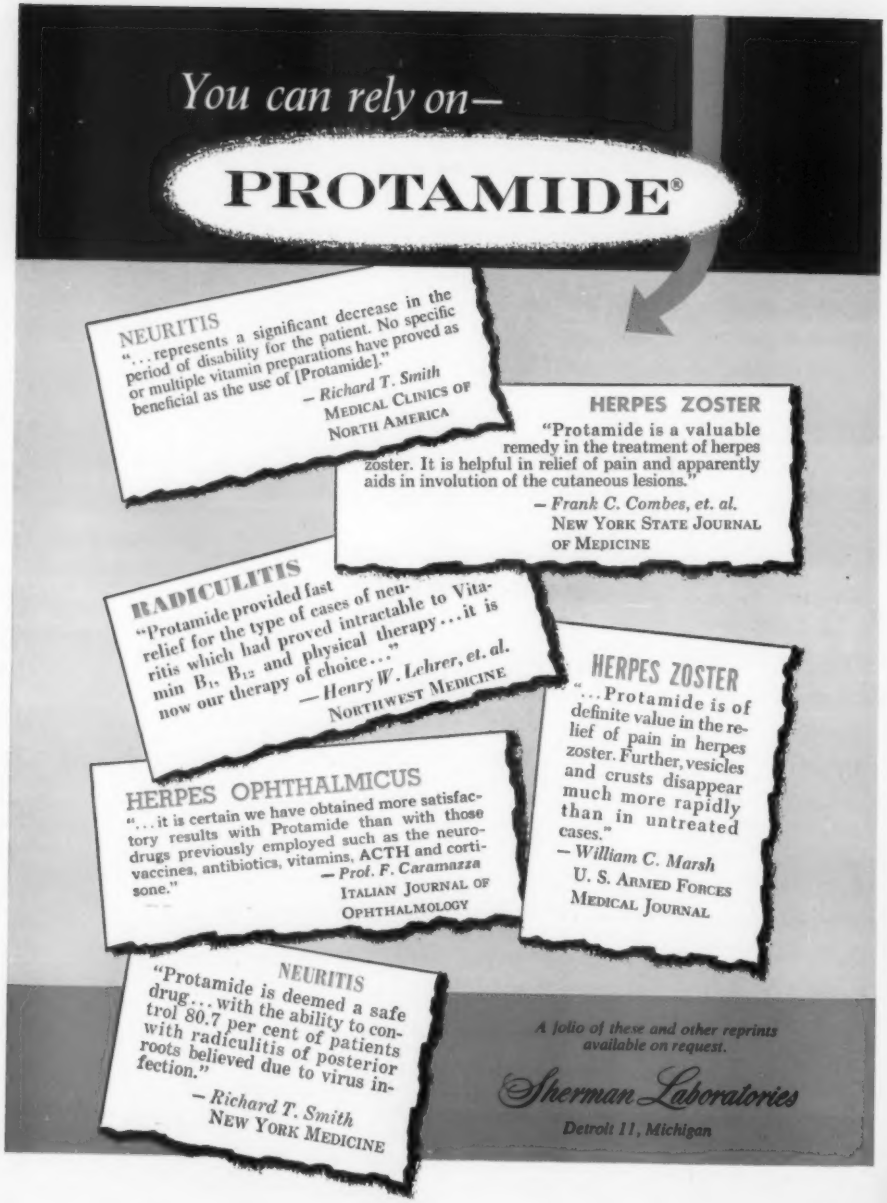
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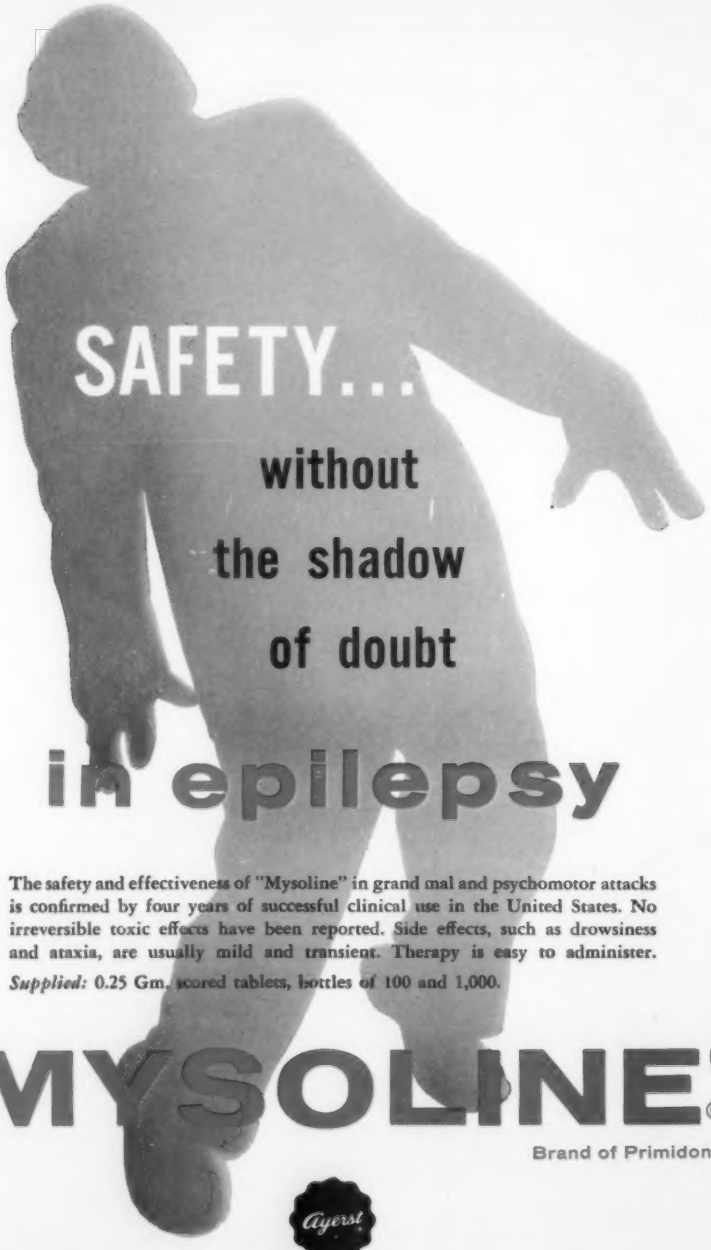
NEUROLOGY is published monthly at 84 South Tenth Street, Minneapolis 3, Minnesota, by LANCET PUBLICATIONS, INCORPORATED. Subscription rate: $12.00 a year, $1.00 a copy; outside the United States $13.00 a year, $1.10 a copy. Entered as second class matter at the postoffice at Minneapolis, January 23, 1951.



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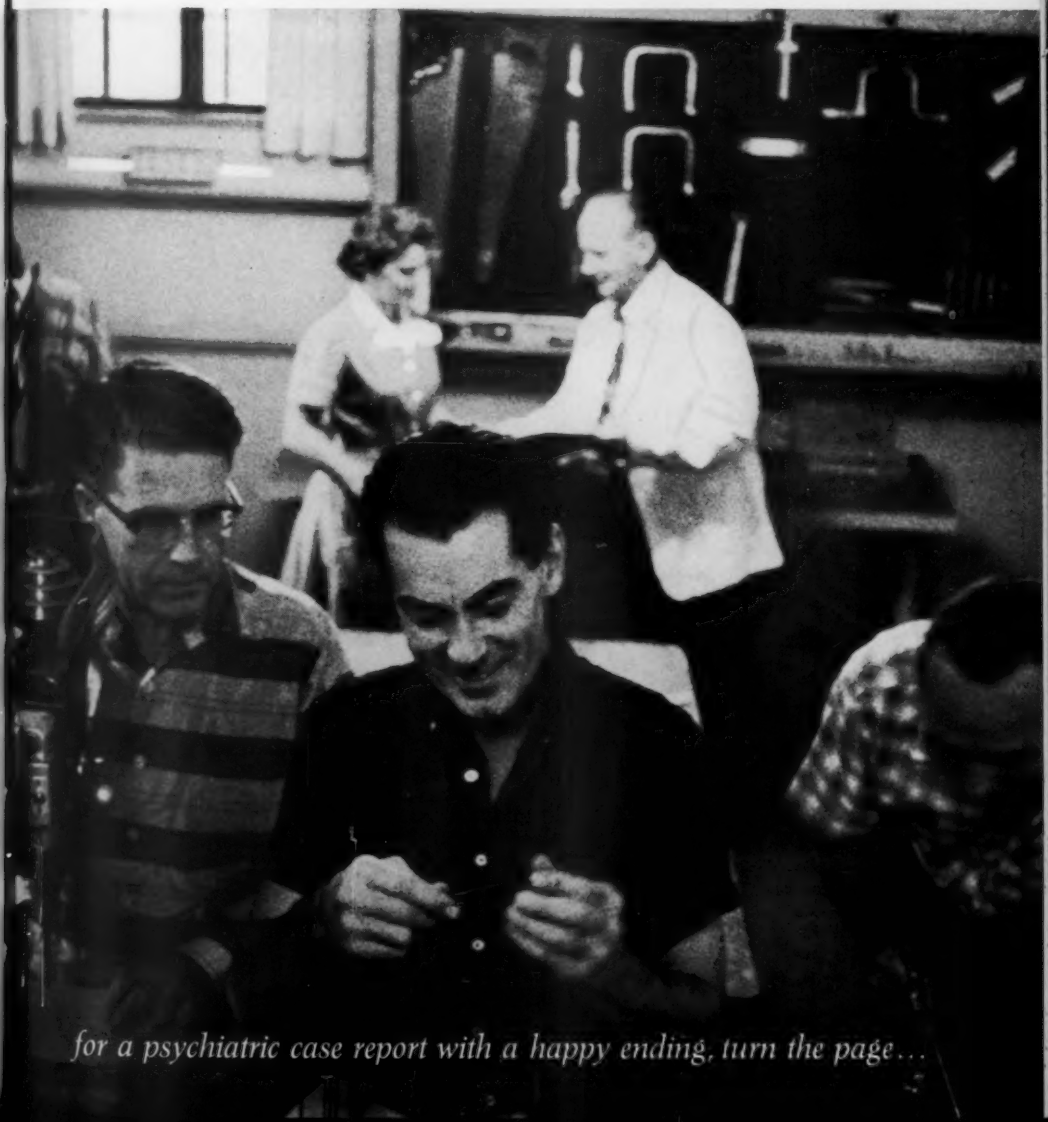

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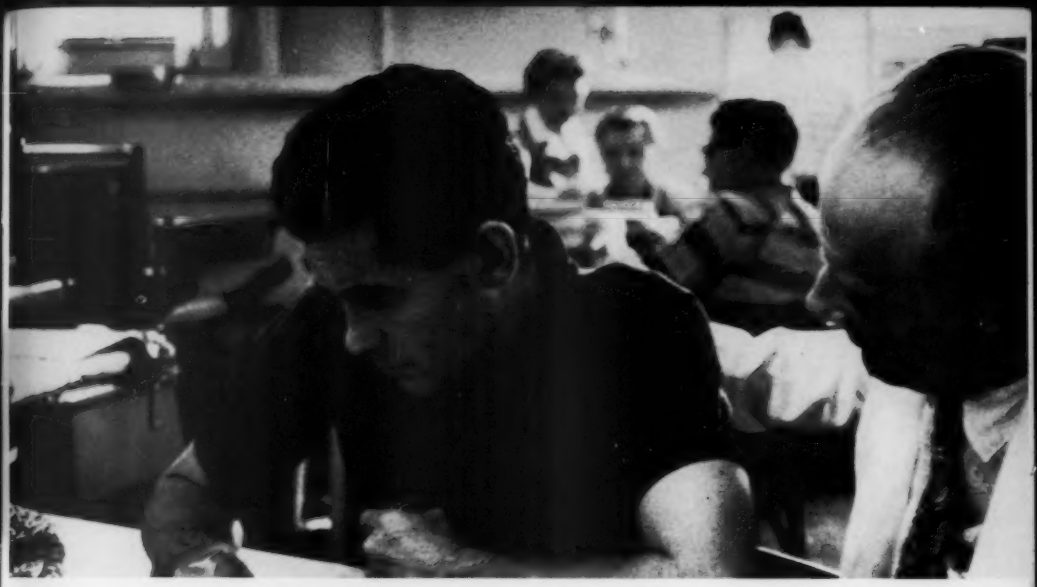

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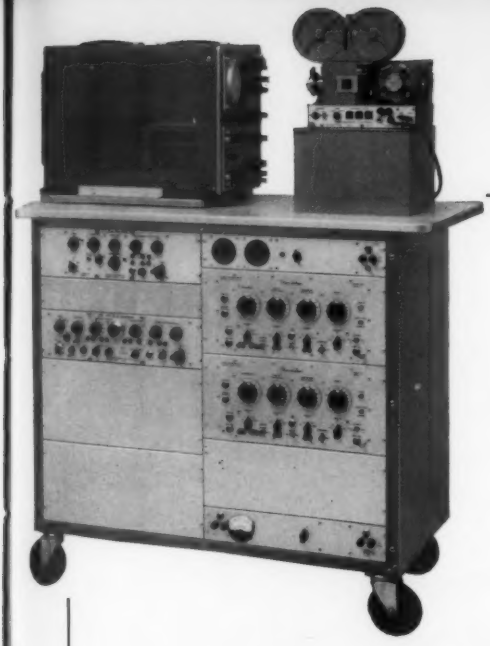

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Ligamentous strains	8	4	4	—	—
Torticollis	3	3	—	—	—
Whiplash injury	3	2	1	—	—
Contusions, fractures, and muscle soreness due to accidents	5	3	2	—	—
		"excellent"			
STUDY 3[5]					
Herniated disc	8	6	2	—	—
Acute fibromyositis	8	8	—	—	—
Torticollis	1	—	—	1	—
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Neurology Volume 9 • Number 2

Clinical and electrographic studies in spontaneous intracerebral hematoma

Daniel Silverman, M.D., Robert A. Groff, M.D., and William Sagen, M.D.

SPONTANEOUS INTRACEREBRAL HEMATOMA, a nontraumatic, circumscribed hemorrhage within the substance of the brain, has been well described in the literature.[1–12] Although subsumed under the category of intracranial hemorrhage in the recently published article, "Classification and Outline of Cerebrovascular Diseases,"[13] we feel that intracerebral hematoma, while rare, is sufficiently distinctive to be considered as a clinical entity. There has been little notice of the electroencephalographic findings (they have not been reported on at all in the English literature). Therefore, 11 cases of spontaneous intracerebral hematoma, all with preoperative electroencephalograms and all but one verified at operation, will be presented in this paper, and an attempt will be made to correlate the clinical and electrographic features.

CLINICAL FEATURES

Although not stressed by previous reports, the onset and course of the syndrome may be acute, subacute, or chronic.

• Acute onset is usually ushered in with violent headache, followed by varying degrees of disturbance in consciousness and focal neurologic signs; convulsions are occasionally noted. In general, the greater the initial impairment of consciousness, the poorer the prognosis. Blood in the subarachnoid space may suggest ruptured aneurysm or noncircumscribed cerebral hemorrhage.

• Subacute onset is characterized by a gradual progression of focal neurologic signs over a period of several weeks to two months. Mild to moderate headache, which, when localized, points toward the site of the lesion, is usually present and, at times, focal convulsive phenomena can be seen. Differential diagnosis from cerebral thrombosis with edema, subdural hematoma, brain abscess, and, especially, brain tumor is often difficult to make preoperatively. Hence, contrast medium studies are usually undertaken.

• With chronic onset and course, convulsive phenomena may dominate the picture, and it may be several years before a lesion is suspected.

The hematoma is usually located in the frontal, temporal, or parietooccipital lobes, ex-

From the departments of Neurology and Neurosurgery, Graduate School of Medicine, Graduate Hospital of the University of Pennsylvania.

Technical assistance in this study was given by T. Sannit and S. Piwoz.

SUMMARY OF DATA ON 11 PATIENTS

Case	Sex	Age	History (Duration)	Signs	Contrast studies	Preoperative electroencephalogram	Operation	Etiology	Preoperative diagnosis; results
1*	F	39	Hypertension, seizures, and unconsciousness (one day)	Right hemiparesis, xanthochromia, and cerebrospinal fluid under increased pressure		Focal slow suppression left temporal		Unknown	Died
2	M	49	Headache, dizziness, and vomiting (three days)	Left hemianopia, left central facial, papilledema and cerebrospinal fluid bloody and under increased pressure	Tapped in ventriculogram	Focal slow left occipitoparietal	10 cc. and 6 cc. removed; 2 cm. deep	Unknown	Preoperatively: aneurysm; improved
3	M	48	Psychotic behavior and headache (two weeks)	Confusion, papilledema, left hemiparesis(?), and bloody cerebrospinal fluid	Arteriogram: Right frontal mass	Focal and general slow right frontal	90 cc. removed; 3 cm. deep; right frontal	Aneurysm of anterior communicating artery	Preoperatively: aneurysm; died twenty-two days postoperatively
4*	F	30	Hemiparesis and mild headache (three weeks)	Left hemiparesis and normal cerebrospinal fluid	Pneumoencephalogram: Right temporoparietal mass	Focal slow right frontal	45 cc. removed; 2.5 cm. deep; right frontal	Melanoma	Preoperatively: brain tumor suspect; died one year later
5	M	66	Hemiparesis, mild headache, and jacksonian seizures (three weeks)	Left hemiparesis and hemihypalgesia and left hemianopia	Arteriogram: Right parietal mass; tapped in ventriculogram	Focal slow right parietal	30 cc. removed; 2 cm. deep; right parietooccipital	Unknown	Preoperatively: brain tumor suspect; improved
6	M	49	Left hemiparesis, somnolence, and mild headache (three weeks)	Left hemiparesis, left central facial paresis, and normal cerebrospinal fluid	Ventriculogram: Right frontotemporal mass	Focal slow right frontotemporal	45 cc. removed; 0.5 cm. deep; right frontal	Unknown	Preoperatively: brain tumor suspect; improved
7*	F	56	Previous strokes, headache and vomiting, and jacksonian seizures (three weeks)	Mentally dull, with right hemiparesis and papilledema	Tapped in ventriculogram; left parietooccipital mass	Focal and general slow left temporoposterior	60 cc. removed; 1.5 cm. deep; left temporoparietooccipital	Venous anomaly	Preoperatively: brain tumor suspect; improved
8*	F	35	Seizures, aphasia, mild headache, and memory difficulty (one and a half months)	Negative on first admission; right hemianopia	Arteriogram: Left temporal mass	Focal slow left temporal	90 cc. removed; 1.5 cm. deep; left temporal	Unknown	Preoperatively: brain tumor; metastatic; improved
9	M	65	Hemianopia, aphasia, mild headache, and hemiparesis (two months)	Right hemianopia, right hemiparesis, aphasia, and normal cerebrospinal fluid	Tapped in ventriculogram	Focal and general slow left occipitoparietal	30 cc. removed; 2 cm. deep; left occipitoparietal; tumor removed later	Metastatic cancer	Preoperatively: brain tumor suspect; died eight months later
10*	M	3½	Seizures, left headache, and left hemiparesis (two years)	Left hemiparesis and left central facial paresis; cerebrospinal fluid contained 25 lymphocytes per cubic centimeter	Pneumoencephalogram: Right frontoparietal mass	Focal slow and spike wave right frontal	60 cc. removed; 3 cm. deep; right frontal	Cavernous angioma	Preoperatively: astrocytoma; improved
11*	F	25	Seizures and aphasia (nine years)	Right hemianopia, right central facial paresis, and normal cerebrospinal fluid	Pneumoencephalogram: Left parietal cyst(?)	Focal sharp and spike wave left parietooccipital	50 cc. removed; 0.5 cm. deep; left parietooccipital	Venous anomaly	Preoperatively: brain tumor suspect; improved

*Complete case histories of these patients appear in the text.

cept in the aged patient when leakage from an atheromatous artery is more likely to be found in the region of the internal capsule, basal ganglia, or pons. At operation, the cortex overlying the hematoma appears avascular, varying in color from a yellowish orange to a brownish red, and the gyri in the involved area appear widened. The brain feels softer than normal with a cystic or fluctuant quality to palpation. The hematoma may lie at any depth, from 0.5 to 7 cm., and varies considerably in size. It may contain varying amounts of liquid blood, solid clot, or both, with necrotic brain. The longer the lesion has been present, the more the blood is liquefied. Etiologic factors include minute cerebral angiomas, varices, arteriovenous malformations, aneurysms, atheromatous arteries, primary and metastatic brain tumors, blood dyscrasias, and other causes. In many cases, the specific cause cannot be found at operation, the vascular malformation having been destroyed or obscured by the hemorrhage.

In this series, 1 patient had an acute onset, 8 subacute, and 2 a chronic course. The clinical pictures were in all cases typical; examples of each type are given below. Hematomas were located in the frontal lobe in 4 patients; in the temporal lobe in 2; in the temporal extending into the occipital lobe in 1; and in the parietooccipital lobe in 4. In 4 patients, the hematoma was tapped during ventriculography. The depth of the hematoma varied between 0.5 and 3 cm. from the cortex; the volume between 15 and 90 cc. Preoperative diagnosis in 8 patients was suspected tumor and in 2 cases, aneurysm, but the known etiologic factors turned out to be venous anomaly in 2 patients, aneurysm in 1, cavernous angioma in 1, melanoma in 1, and metastatic carcinoma in 1 (Table 1).

Follow-up studies revealed that 2 patients died during their first hospitalization from the illness and 2 died subsequently of the malignant lesion responsible for the hematoma. Upon reexamination one to three years after operation, 4 patients were improved and, in these patients, seizure phenomena were controlled by anticonvulsant medication. Indirect information concerning the remaining patients indicated that 2 were well and 1 had further neurologic difficulty.

ELECTROENCEPHALOGRAPHIC FEATURES

All electroencephalograms were taken on an 8-channel Model III A Grass machine; 15 scalp electrodes, covering the frontal, central, parietal, occipital, anterior temporal, temporal, and posterior temporal areas of each hemisphere and the vertex, were used, and scalp-to-scalp and scalp-to-ear linkages were employed. Activations by sleep, hyperventilation, apnea, and photic stimulation were used whenever possible.

Electroencephalographic pictures of focal delta and theta activity, most often seen with intracranial mass lesions, were present in 8 of the 11 patients. It was notable that the dysfunction appeared mostly in the 4 to 7 per second range together with base line sways; in 5 of the 8 patients, these were sharply localized with minimal spread and, in the remaining 3, whose electroencephalograms still showed a focus of maximal abnormality, there was some bilateral theta activity and slowing of alpha. Sleep state recordings were obtained in 3 of these 8 patients, and, in each instance, there was persistence of the slow wave focus in sleep and distortion of the sleep state potentials. Hyperventilation and apnea accentuated focal delta activity in 3 patients. In 1 patient observed for a month before operation, the electroencephalographic dysfunction increased. It was possible to obtain postoperative follow-up electroencephalograms in 2 patients; the dysfunction did not disappear but changed to that of spike-wave focus.

These patients usually had subacute onsets with progression of symptoms less than two months before hospitalization. Age distribution ranged from 30 to 65 years. In 6 of the 8 patients, symptoms or signs of increased intracranial pressure were present, suggesting expanding mass lesions; 1 had had two previous strokes before the current acute episode with associated papilledema. The 2 patients without symptoms or signs of increased intracranial pressure presented clinical pictures suggestive of cerebrovascular thrombosis. In 4 of the hematomas, occurring in the occipitoparietal regions, the cystic cavities were traversed during ventriculography. In all patients, the localization by electroencephalography was accurate.

*Complete case histories of these patients appear in the text.

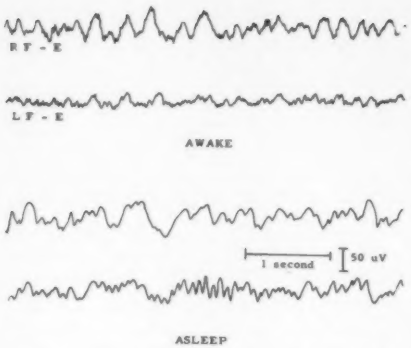

Fig. 1. *(Case 4)* Preoperative electroencephalogram showing right frontal delta focus, persisting in sleep, and suppression of sleep spindles

CASE HISTORIES

*Case 4.** This 30-year-old woman complained of incoordination and weakness of her left extremities for two weeks before admission. Neurologic examination revealed a left hemiparesis. Spinal fluid pressure and contents were normal. The electroencephalogram (Fig. 1) revealed a right frontal delta focus, which persisted in sleep, with suppression of sleep spindles. A pneumoencephalogram indicated a right frontoparietal mass. At operation, the right frontal convolutions were widened, discolored, dimpled, and soft. At a depth of 2.5 cm., a cyst filled with 45 cc. of brown blood and clot was encountered. No explanation was found for the bleeding; however, in the microscopic section of the clot, a small nubbin of melanotic tissue was discovered. The patient improved temporarily, but died about a year later of the melanoma.

Case 7. A 56-year-old woman had a history of two right-sided strokes, three and two years previously, after which she regained full function. Two weeks before hospitalization, she had some jacksonian twitching of her right face, hand, and arm. Neurologic examination showed a partial motor aphasia, a right hemiparesis, and papilledema. The electroencephalogram (Fig. 2*A*) revealed a left posterior temporal and temporal delta focus which persisted into sleep, together with suppression of sleep state potentials. Ventriculography, during which 2 cc. of blood was obtained on the left side, suggested a left parietal mass lesion. At operation, the left temporooccipital cortex showed a brownish discoloration and was fluctuant. At a depth of 1.5 cm., a large organized clot and about 60 cc. of old liquid blood were encountered; at the bottom of the cavity a venous anomaly was discovered. Examination one and one-half years later revealed a left temporal slow and spike-wave focus (Fig. 2*B*). There had been no seizures, but the patient had a mild right hemiparesis and ataxia.

Case 8. A 35-year-old woman had a grand mal seizure followed by a transient motor aphasia of several hours' duration one week before admission. Since the seizure, she had had a severe headache and some difficulty with memory. Neurologic examination was negative. The first electroencephalogram showed a left temporal delta focus (Fig. 3*A*). She was observed on conservative treatment until a month later when the electroencephalogram showed increased abnormality (Fig. 3*B*). Neurologic examination then revealed a right homonymous hemianopsia. Arteriograms indicated a left temporal mass lesion, and, at operation, the left temporal convolutions were discolored and softened. At a depth of 1.5 cm., the hematoma cavity was entered; it contained 90 cc. of old blood and clot. No explanation for the bleeding was evident. Examination two and one-half years later revealed a left temporal spike and spike-wave focus (Fig. 3*C*). She had remained well except for one seizure since the operation.

Electroencephalograms with focal sharp waves, spikes, and occasional spike-waves together with focal slowing were obtained from 2 patients. Clinically, these cases were characterized by a chronic course, primarily with convulsive seizures. Since they are of interest, they are reported below.

Case 10. A 3½-year-old boy, with grand mal convulsions for one and one-half years before ad-

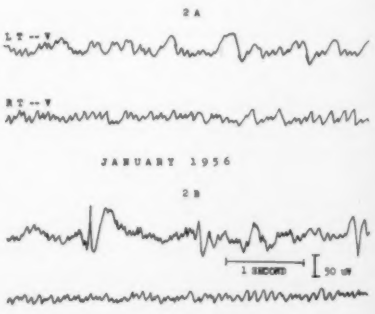

Fig. 2. *(Case 7) (A)* Preoperative electroencephalogram with left posterior temporal and temporal delta focus, persisting in sleep, with suppression of sleep state potentials. *(B)* One and one-half years postoperatively, showing left temporal slow and spike-wave pattern

*Numbering of cases corresponds with the table.

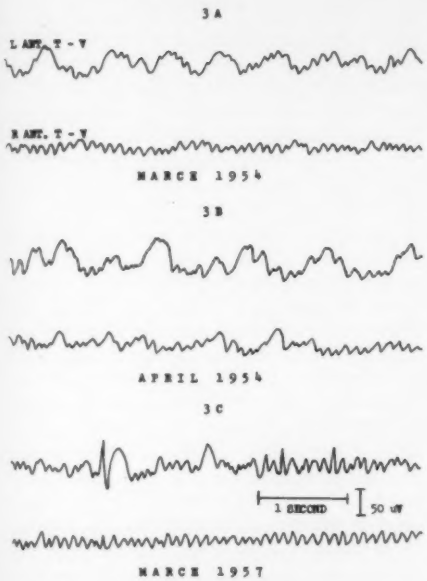

Fig. 3. *(Case 8) (A)* Preoperative electroencephalogram showing left temporal delta focus. *(B)* One month later, increased abnormality. *(C)* Two and one-half years postoperatively, left temporal spike and spike-wave focus

mission, was partially controlled by medication. Over the two months before admission, he developed headaches, drowsiness, left jacksonian seizures, and some left-sided weakness. Neurologic examination revealed a left hemiparesis and left Babinski sign. Cerebral spinal fluid contained 25 lymphocytes per cubic centimeter. The electroencephalograms (Figs. 4*A* and *B*), observed over several months, showed increasing focal delta, spike, and spike-wave activity in the right frontal area; the latter was more pronounced during sleep. A pneumoencephalogram indicated a right frontal mass lesion. At operation, the middle frontal convolution was discolored and soft. At a depth of 3 cm., a large cavity containing 60 cc. of organized clot and blood was encountered; microscopic section of the clot revealed a cavernous angioma. Examination three years later revealed a right frontal spike-wave focus during sleep (Fig. 4*C*); clinically, he was well, except for a mild weakness on the left, and there was no recurrence of seizures.

Case 11. This 25-year-old woman gave a history of a mild head trauma at age 16 which was followed by a grand mal seizure the next day and by mild headaches for six months. Seizures recurred intermittently and were controlled by anticonvulsants. Over the next seven years, 4 pneumoencephalograms and 1 arteriogram, made at other hospitals, were interpreted as normal. For five months before admission, the seizures increased despite heavy medication and with some there was transient aphasia. Neurologic examination revealed only a right central facial paresis. The electroencephalogram five months before admission (Fig. 5*A*) showed left parietal focal sharp waves; on admission, this focus had increased and the electroencephalogram also showed spike-waves (Fig. 5*B*). Exploratory operation revealed that the left parietooccipital convolutions were widened, yellowish, and fluctuant. At a depth of 0.5 cm., a cystic cavity filled with 50 cc. of red-orange fluid was found. Thin-walled vessels, a venous anomaly evidently the source of the bleeding, were at the bottom of the cavity. Examination two and one-half years later revealed a left posterior temporal spike and spike-wave focus on the electroencephalogram (Fig. 5*C*); there had been only one seizure since operation.

Case 1. Although not proved, this 40-year-old woman is our only patient with a suppression type of electroencephalographic abnormality and with

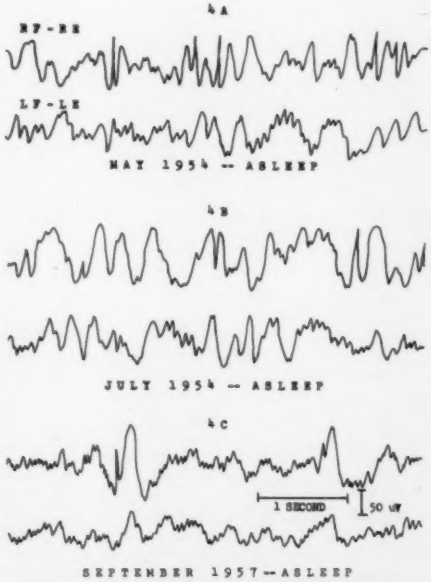

Fig. 4. *(Case 10) (A and B)* Electroencephalograms over several months, showing increasing focal delta, spike, and spike-wave activity in right frontal area, the latter more pronounced in sleep. *(C)* Three years postoperatively, right frontal spike wave focus during sleep

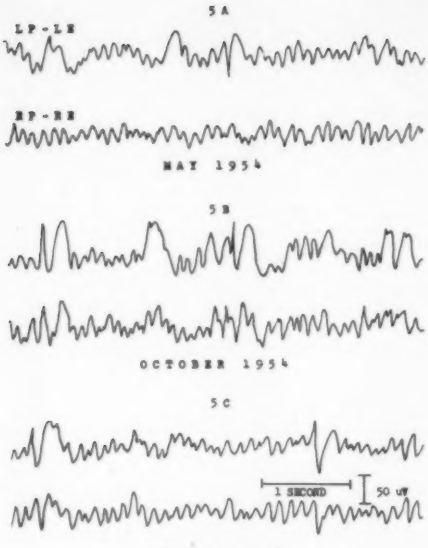

Fig. 5. *(Case 11) (A)* Electroencephalogram five months before admission showing left parietal focal sharp waves. *(B)* On admission, the left parietal focal sharp waves are increased and spike waves are seen. *(C)* Two and one-half years later, left posterior temporal spike and spike-wave focus

an acute onset. She had a long previous medical history of treated lues, hypertensive cardiovascular disease, alcoholism with cirrhosis of the liver, and mild diabetes. On the morning of her illness, she complained of severe headache, lapsed into unconsciousness, and began having continuous right-sided jacksonian convulsions. On admission to the hospital that evening, a right flaccid hemiplegia and right Babinski sign were noted. Cerebrospinal fluid was bloody and under increased pressure (400 mm. of water). Vigorous anticonvulsant medication stopped the seizures after two days but she continued to have a severe headache, partial aphasia, and right hemiparesis. The electroencephalogram (Fig. 6) showed a left temporal slow wave focus with marked suppression of potentials on the left. Conservative treatment was decided upon, but, some weeks later, she developed an acute pneumonitis and succumbed; a brain autopsy was not performed.

DISCUSSION

The summary of data on these 11 patients suggests a division of the spontaneous intracerebral hematoma syndrome into 3 clinical and corresponding electrical types. These divisions are indicated in the table with dotted rules. The first category, represented by the first case, is characterized by an apoplectic or acute onset and a slow wave focus with suppression of potentials in the electroencephalogram. The second category, the majority, represented by the next 8 cases, is characterized by a subacute course often simulating brain tumor and a well-localized slow wave (usually theta) focus in the electroencephalogram. The third category, represented by the last 2 cases, is characterized by a chronic course and convulsive manifestations and focal spikes and spike-waves in the electroencephalogram. It is interesting that the postoperative dysfunction remaining in those patients whom we were able to observe was of the spike-wave focus type. This suggests that, when a lesion is contracting, spike waves are likely to be produced in the electroencephalogram. Perhaps, with chronic intracerebral hematoma, this contracting tendency results in the chronicity, electrographic spike-wave patterns, and seizure phenomena. A further inference is that anticonvulsant medication is indicated postoperatively in all cases of spontaneous intracerebral hematomas. It would be of importance in future cases to observe the postoperative course closely with the electroencephalograph to determine how long it takes for spike waves to appear.

Electroencephalographic study – particularly serial electroencephalography – gains in im-

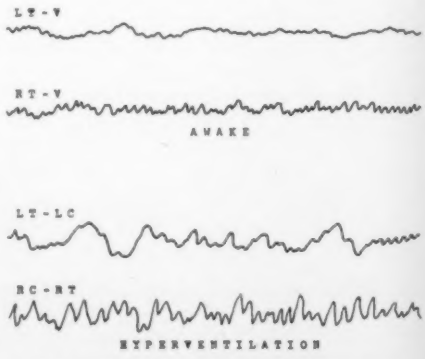

Fig. 6. *(Case 1)* Left temporal slow wave focus with marked suppression of potentials on the left

portance when the differentiation between a cerebral thrombosis or other non-space-taking lesions and a mass lesion is a problem. In 3 patients, increasing electroencephalographic abnormality helped the clinician decide on contrast medium studies or exploratory operation. In 2 other patients, a clear-cut delta focus on the electroencephalogram helped the decision for ultimate operative approach. The sleep changes were entirely consistent with a previously published investigation[14] on the significance of these changes in brain tumors; in this study, the persistence of the delta focus into sleep and the suppression of sleep spindles occurred with hematomas less than 3 cm. from the convexity of the cortex, which in all cases was grossly involved in the pathologic process.

Review of the European literature reveals that Paillas and associates,[15] Gros and Minvriella,[16] and Corsino and associates[17] have described the electroencephalographic features of 41 patients with intracerebral hematomas. As in our series, the predominant abnormality – found in 21 patients – was focal theta and delta activity; in 9 of these patients, some bilateral disturbance was also noted. The next most common feature was focal spikes and spike waves, found in 12 patients. In 5 patients there was suppression in the central region of a delta focus, and in 3 there were bilateral bursts of delta activity, interpreted as indicative of compression phenomena and therefore of surgical emergency. It can be seen that these results are highly compatible with our own. Unfortunately, the authors gave no detailed description of the clinical aspects so that we were unable to test the above-mentioned suggestion on the correlation of clinical course and electroencephalographic pattern on their patients.

SUMMARY AND CONCLUSIONS

Spontaneous intracerebral hematomas give rise to 3 types of electroencephalographic abnormalities:

1. *Focal theta and delta activity.* This phenomenon is mostly well localized, without much bilateral representation. Associated with a subacute clinical course, such activity often simulates a brain tumor.

2. *Focal spikes and spike-waves together with slowing.* This pattern occurs less frequently and is associated with a chronic clinical course and chiefly convulsive manifestations.

3. *Suppression together with focal slowing* is occasionally seen. It is associated with an apoplectic or acute clinical course.

It is concluded that the electroencephalogram is a helpful adjunct in the diagnosis and localization of intracerebral hematoma.

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Some physiologic implications of craniopharyngiomas

Edgar A. Kahn, M.D.

UNDUE PESSIMISM still exists among neurosurgeons as to the efficacy of treatment of craniopharyngiomas.[1–3] A radical, though not necessarily total, removal of any craniopharyngioma is fraught with danger, but my results with the surgical treatment of these tumors have improved so much with the advent of cortisone[4,5] that I am reporting this experience in the hope of influencing others into a more aggressive approach to the removal of these tumors.

I should like to report 18 consecutive primary operations in my own series. Cortisone was used preoperatively in all but the first 2 patients. Of the operations, 17 were radical. Total excision appeared to have been accomplished in 6 patients, but recurrence is known to have taken place at the end of eight years in 1. Time alone or postmortem examination will determine whether or not total excision was actually accomplished.

Total removal of a craniopharyngioma is possible as shown in the case of a 6-year-old girl who was operated upon by Peet[6] in 1927. This girl did well for four years and then died of an acute streptococcal infection of the pelvis. Autopsy revealed no evidence of recurrent tumor.[7] In 1938,[8] I operated upon a 3-year-old girl for what proved to be a surprisingly easy removal of a calcified craniopharyngioma. This girl is now a graduate nurse at the University of Michigan Hospital and shows no detectable abnormality.

Of 18 consecutive operations for craniopharyngiomas over a ten-year period, results were excellent in 9 and poor in 3; 6 eventually died after their return home, but there were no deaths after the 18 *primary* operations for craniopharyngioma. Cortisone was given preoperatively in 16 instances. Experiences which may aid in the handling of these patients and throw light on the anatomy and physiology of the hypothalamohypophyseal system will be detailed in a discussion of individual cases.

CASE REPORTS

Case 1. A 4-year-old girl was given the usual preoperative preparation with cortisone. A large tumor, including a 50-cc. cyst, was removed subtotally. The maximum postoperative temperature was 102.8° F. The patient did well for six weeks and then commenced to show evidence of increased intracranial pressure. A Torkildsen operation was performed on May 22, 1952, but, for some unknown reason, preoperative cortisone was not administered. On the morning of the second postoperative day, the child went into circulatory collapse and was found to have a temperature of 108° F. Adrenocortical extract and cortisone were administered; this resulted in some improvement, but twenty-four hours later, the child's temperature was 107° F. She died the following day.

In the 16 patients given cortisone preoperatively for the primary operation, the highest temperature recorded was 104.2° F. In one patient with known panhypopituitarism, death took place after a second attempt to remove the tumor, the temperature reaching 108° F. in spite of preparation with cortisone (Fig. 1). Irrespective of this one case, however, no doubt exsits that cortisone in some way exerts an antipyretic effect after operative procedures involving the hypothalamus, although the mechanism is still unknown. It may be that the cortisone, by combating circulatory collapse, forces the blood from the splanchnic area to the periphery where heat can be dissipated. This will be discussed in more detail later.

Case 2. A 44-year-old mother of 3 children came to the University Hospital because of visual disturbance, severe headaches of three months'

From the Department of Surgery, Section of Neurosurgery, University Hospital, Ann Arbor, Mich.
Presidential Address, presented at the annual meeting of the Society of Neurological Surgeons, Durham, North Carolina, April 19, 1958.

duration, and hypersomnolence, with periods of sleep lasting from eighteen to forty-eight hours.

This patient was discovered to be diabetic in 1953. Her father and two aunts were also diabetic. In April of 1957, one of her physicians suggested that her diabetes was "not too difficult to control," with 60 units of NPH insulin in the morning and 25 units in the evening. The patient was seen by Dr. John M. Thompson of St. Petersburg, Fla., who discovered a bitemporal hemianopsia. It was his opinion that this patient had a surgical lesion in the region of the hypothalamus. An arteriographic study suggested to Dr. Thompson that a suprasellar tumor was present, and the patient was referred to the University Hospital.

Examination revealed a cheerful woman, 5 ft. ¾ in. tall, weighing 192 lb. Roentgenographic examination of the skull revealed no evidence of any disturbance in the region of the sella turcica. Bitemporal hemianopsia with splitting of the macular area was confirmed. Testing revealed 17-ketosteroids to be 3 mg. per twenty-four hours and 17-urinary hydroxycorticosteroid 5.8 mg. per twenty-four hours. Since she had recently had an arteriogram, thyroid function could be studied only by basal metabolic rate, which was — 8%; pulse was 90. Total serum cholesterol was 217 mg. per cent. The fasting blood sugar was 112 mg. and 120 mg. per cent during the first two days after hospital admission. Her diabetes was controlled by 40 units of NPH insulin in the morning and 10 units of PZI in the afternoon. Although the patient did not show evidence of hypopituitarism, she was prepared for operation in the usual manner with cortisone.

A right-sided osteoplastic craniotomy was performed May 27, 1957, and a cystic craniopharyngioma was found to lie in front of and beneath the chiasm; 7 cc. of fluid was aspirated from the tumor. The mass was then removed from beneath the chiasm and the region of the hypothalamus and was measured at approximately 2 by 2 by 2.5 cm.

For twenty-four hours, the patient did well. Her temperature then rose to 104° F., the pulse to 160, and the respiration to 40. Her blood pressure was unobtainable. At this time, she was placed on an ice mattress. Her temperature actually rose slightly, and the entire posterior surface of her body became ice cold to the touch. The ice blanket was removed immediately. The head was lowered, the skin was rubbed briskly with rough towels, and she was swathed in warm blankets. As soon as surface warmth was reestablished, alcohol was placed on the skin surface and allowed to evaporate. Inasmuch as the patient was in circulatory collapse, it was believed that she was not benefiting from her intramuscular cortisone. The patient was then given 500 cc. of whole blood, 100 cc. of 50% glucose, and 50 mg. of hydrocortisone intravenously. Although all extremities had been moving well before the advent of the circulatory collapse, the left face, arm, and leg were observed to be paralyzed.

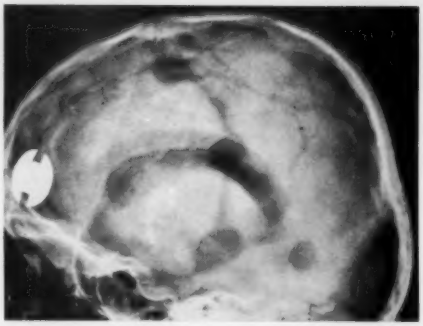

Fig. 1. Diffuse calcification in infiltrating craniopharyngioma without hydrocephalus. Operative procedures are useless in such cases. Patient died after second attempt at removal with temperature of 108° F. despite cortisone.

At 7:45 P.M., she had been placed on the ice blanket. At 8:00 P.M., the ice blanket was removed and the intravenous fluids started, rubbing commenced, and blankets and hot water bags placed around the patient. By 9:30 P.M., her blood pressure was 140/100, pulse 120, and respiration 34. By 10:00 P.M., the patient was responsive and took small sips of orange juice. The hemiplegia had almost disappeared by the next morning and the patient was in a much improved condition. She was discharged twenty-two days after surgery.

The patient did well on 35 mg. of cortisone daily, 35 units of NPH insulin, and 1 cc. of Pitressin every few days until the late fall when she began to demonstrate increasing lethargy, loss of energy, and intolerance to cold.

She returned to the hospital on February 21, 1958 with obvious gross myxedema and uncontrolled diabetes insipidus of which she seemed unaware. She had been taking Pitressin but would often go for ten days without it.

Twenty-four-hour uptake of I^{131} was 5.3%. After 10 units of thyroid-stimulating hormone, the twenty-four-hour uptake was 15.8%. The interpretation was that this patient had myxedema and a subnormal response to the thyroid stimulating hormone, but it was proved that her thyroid gland was functioning. There now appeared to be no doubt that she had panhypopituitarism, and she was placed on 3 gr. of thyroid extract a day, 35 mg. of hydrocortisone, 5 units of Pitressin tannate in oil every Monday and Thursday, and 10 units of NPH insulin daily. With this medication, symptomatic improvement was remarkable. It is interesting to note that the diabetes mellitus had ameliorated considerably after the operation, in spite of full replacement of the adrenocortical steroids. This change would suggest that growth hormone activity was decreased postoperatively.

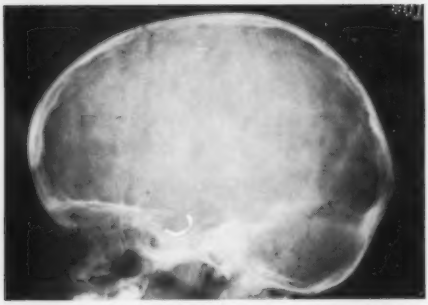

Fig. 2. *(Case 3)* Calcification in intrasellar portion of craniopharyngioma (Retouched)

Fig. 3. *(Case 3)* Showing roentgenographic evidence of total removal of intrasellar portion of craniopharyngioma

Before cortisone was employed preoperatively, circulatory collapse was common during and after operations involving the region of the hypothalamus. This was particularly noted when previous hypopituitarism with secondary hypoadrenocorticism was present. Normally, during the stress of surgery, circulatory collapse is prevented by the increased release of hydrocortisone and by the effect of noradrenalin with the permissive action of hydrocortisone. If ACTH or hydrocortisone is lacking because of [1] hypopituitarism or hypoadrenalism or [2] the trauma of operation to the hypophysis or the ACTH-stimulating center of the hypothalamus in normal individuals, sufficient hydrocortisone may not be produced to prevent circulatory collapse. It is for this reason that all patients who are to have operations in the region of the sella turcica should be prepared with cortisone and be given intravenous hydrocortisone if there is evidence of impending collapse.

In cases of circulatory collapse, a pooling of blood occurs in the splanchnic area as it does in shock. As a consequence, the blood flow to the periphery is diminished and heat is not adequately radiated from the body surface. The body surface is therefore cool to the touch while the internal temperature may be very high. One can thus see why high temperatures may be associated with circulatory collapse in hypopituitarism or hypoadrenalism.

There is a more important mechanism whereby the body temperature may be raised abnormally in operations involving the anterior hypothalamus;[9] a center in the anterior hypothalamus causes sweating and inhibits the vasoconstrictor center of the posterior hypothalamus in order that peripheral vasodilation can take place. High body temperature is normally precluded by peripheral vasodilation and by the evaporation of the individual's own sweat.

It is completely illogical, therefore, to chill an already cold body surface with ice which will only produce further peripheral vasoconstriction. On the other hand, it *is* logical to increase the body surface circulation by increasing blood volume through transfusion and by the application of mild heat and local friction to promote vasodilation of the extremities. When circulatory collapse occurs, intramuscular cortisone is not adequately absorbed. For this reason, hydrocortisone should be administered intravenously.

Case 3. A 4-year-old girl was operated upon for what was believed to be a total removal of an intrasellar cystic craniopharyngioma (Figs. 2 and 3). Aside from a transient diabetes insipidus, her convalescence was quite uneventful. Microscopic examination revealed that normal pituitary gland substance had been inadvertently removed with the tumor. Six months later, the child was in a tourist camp with her parents when she became ill; the condition was diagnosed tentatively by the local physician as some type of food poisoning. The child did not awaken in the morning and was taken to the local hospital where she remained unconscious. She died the next day. The

local physician stated that he had not considered that the child might have a hypoglycemia resulting from a lack of food intake and that he was chagrined that he had not obtained a blood sugar determination.

Several years before, I had made the same mistake, though fortunately the condition was recognized by a medical colleague. The patient was a child[8] who was known to have been blind at 9 months of age; a huge craniopharyngioma had been removed when he was 33 months old. Five months later, the child returned to the hospital in coma. It was my opinion that the symptoms resulted from a recurrence of the tumor, in spite of the fact that a gross total removal might have been accomplished. The child was seen by Dr. H. S. Seltzer, who suspected that the coma was secondary to hypoglycemia. The blood sugar determination was reported at 5 mg. per cent. The child revived miraculously after administration of intravenous glucose and is attending blind school today, six years after the operation.

ACTH normally stimulates the action of the adrenal cortex in the formation of the carbohydrate-regulating corticoid, hydrocortisone, which is essential to the complicated process of gluconeogenesis from noncarbohydrate sources. Gluconeogenesis is one method of counteracting the effect of insulin. If ACTH is absent or diminished as a result of hypopituitarism, a secondary hypoadrenalism will appear. The production of hydrocortisone will then be diminished, and an important method of combating the effects of insulin in lowering blood sugar will be lost. Furthermore, the growth hormone[10] of the anterior pituitary in the presence of adrenal steroids is believed to antagonize the action of insulin and normally tends to elevate the blood sugar levels.

In the normal fasting state, the hydrocortisone stimulates gluconeogenesis to the extent of preventing hypoglycemia. It is easy to see how, under conditions of limited carbohydrate intake in hypopituitarism, serious hypoglycemia could develop and coma result. Case 3, who probably did have food poisoning, undoubtedly died in hypoglycemic coma, for she had been "perfectly well the day before." The patient who was brought out of coma with intravenous glucose when the level of blood sugar was 5 mg. per 100 cc. of blood has had no further difficulty with hypoglycemia over the past six years, but he has been placed on a high protein and carbohydrate diet which tends to maintain the blood sugar at more constant levels than does one rich in carbohydrate alone.

It should be remembered that insulin tolerance tests in the presence of hypopituitarism and primary hypoadrenalism may be dangerous. The insulin tolerance test measures the maximal capacity of pituitary and adrenal response. For this test, Williams[10] advises intravenous injection of 0.1 unit of insulin per kilogram of ideal body weight. In cases where adrenal insufficiency is suspected, Williams suggests that only 0.03 units per kilogram of body weight be used and that the patient be observed carefully before and after the test for hypoglycemic reactions. In 1941, Rowlands and associates[11] described a 44-year-old hypopituitary dwarf with a craniopharyngioma. His weight was 64¾ lb. He was given 5 units of insulin (probably subcutaneously) and 20 gm. of carbohydrate by mouth at the same time. According to Williams, this would amount to 5 times the safe dose of intravenous insulin. This patient developed such severe hypoglycemic convulsions that it was believed he would have died had glucose not been given intravenously.

Case 2 had had severe diabetes for at least four years before her craniopharyngioma was removed. Her daily preoperative dose of insulin had been 85 units. She showed definite disturbance of the posterior hypothalamus preoperatively; she was hypersomnolent and once slept for forty-eight hours and confabulated like a patient with Korsakoff's psychosis. Hypopituitarism, however, could not be demonstrated. Ten months postoperatively, panhypopituitarism proved to be present and the patient was maintained on only 10 units of NPH insulin each morning. That she was performing like a Houssay dog seems quite certain.

Case 4. A 9-year-old boy was admitted to the University Hospital in December of 1957, with a history of headaches, vomiting, convulsive seizures, marked thirst, and high fluid intake. Decreasing vision had been noted during the previous ten months. His parents stated that his personality was "more like a girl's than that of his brothers."

Visual acuity was 20/20 in the right eye and 20/50 in the left. Visual fields showed a temporal

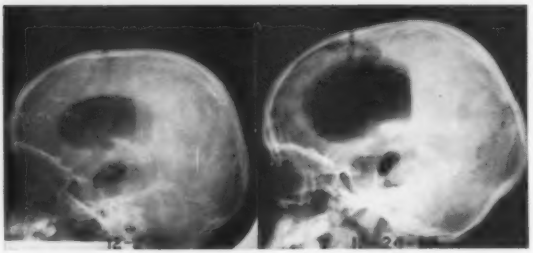

Fig. 4. *(Case 4) Left:* Ventriculogram showing evidence of defect in region of foramen of Monro. *Right:* Spontaneous tension pneumocephalus from operative defect in sella turcica. Air fills the anterior third ventricle and sella turcica showing evidence of gross total removal of tumor.

defect in the right eye. Marked enlargement of the sella turcica with separation of the sutures was present but no suprasellar calcification was noted. Ventriculographic examination revealed dilation of the lateral ventricles with a filling defect in the region of the foramen of Monro. A large, solid craniopharyngioma was removed surgically from the sella turcica and the region of the third ventricle. It was believed that a total removal might have been realized. In an effort to remove the tumor totally, the floor of the sella turcica was extensively cauterized with the Bovie unit.

Diabetes insipidus developed on the second postoperative day, and Pitressin therapy was started on the seventh. Constipation with abdominal distention, believed to have been caused by general body dehydration resulting in excessive reabsorption of water of the stool in the large bowel, had become a problem.

During the third week, the child was up and around but was kept in the hospital in an effort to adjust the dose of Pitressin accurately.

Toward the end of the third postoperative week, a cerebrospinal fluid rhinorrhea developed. A skull roentgenogram (Fig. 4) showed that air completely filled the ventricular system and that the ventricular system was considerably more dilated than had been demonstrated by the original ventriculogram. The ventricle was tapped, air under pressure released, and ventricular drainage instituted. A culture of Streptococcus viridans was obtained. Massive antibiotic therapy was instituted and hydrocortisone given. The wound was reopened, and a large defect leading to the sphenoid sinus was found in the anterior part of the sella turcica. A small amount of residual tumor was discovered when the tuberculum sellae was removed to obtain a better exposure of the area of the cerebrospinal fluid leak. The hole in the sella turcica was plugged with muscle and the wound closed; ventricular drainage was continued for four days.

On the seventh day after the first operation, at which time the boy weighed 45 lb., the fluid output had reached 5,785 cc., the equivalent of 18 liters in a 140-lb. adult. After the second operation, the diabetes insipidus was even more difficult to control, 3 to 4 units of Pitressin being given daily. Constipation and adynamic ileus were severe but were corrected when low serum potassium levels were raised and the potassium depletion corrected. The patient was in an extremely desperate condition involving grunting, tense respiration, generalized rigidity of all muscles, and akinetic mutism. During the second and third weeks after the second operation, the child continued to be in critical condition. In one three-day period, urinary output was 3,710 cc., 4,315 cc., and 4,775 cc., despite doses of intramuscular Pitressin of 6, 6.6, and 7 units. It was noted that the buttocks were indurated because of prolonged administration of large doses of antibiotics and postulated that the Pitressin was being stored in the indurated areas; rotation of injection sites now controlled the diabetes insipidus on 3 units per day. The child gradually recovered completely and returned to the hospital six and one-half months postoperatively in excellent condition, taking thyroid extract and but two units of intramuscular Pitressin tannate in oil every other day.

Case 5. A 28-year-old man entered the hospital because of impotence and failing vision which had developed during the previous year. Flicker fields suggested a bitemporal hemianopsia on the tangent screen. Visual acuity was 20/70 in the right eye and 20/30 in the left. Arteriographic examination showed no evidence of abnormality. Pneumoencephalographic study (Fig. 5) revealed that the cisterna chiasmatis was filled with air, and the films were interpreted as being normal. X-ray therapy was started on the theory that there might be a suprasellar extension of a chromophobe adenoma. Within two months after the x-ray treatment was begun, the vision had returned to 20/25 in the right eye and 20/20 in the left. This visual acuity was maintained for over three months when it started to decrease again. An operation was performed, and both optic nerves and the diaphragma sellae appeared to be normal. A solid craniopharyngioma measuring 2 by 1 by 1 cm. was removed gross totally from beneath a postfixed chiasm. Convalescence (Fig. 6) was uneventful except for the onset of diabetes insipidus. The patient was discharged from the hospital and instructed to take 0.5 cc. of Pitressin tannate in oil every other day. The diabetes insipidus was well controlled by this medication. After the patient had been at home for about two weeks, he suddenly developed severe water intoxication with generalized edema. His wife stated that he had

drunk a large quantity of fluid the day before. The patient was hospitalized in his own home town for three weeks and was desperately ill for the first three days. His local physician wisely discontinued the Pitressin. On his return visit to this hospital in February 1958, two months after his hospitalization for water intoxication, he stated that he was back at work and was taking no Pitressin. His only medication was thyroid extract and testosterone. He had recently experienced an orgasm.

Both of these patients show the postoperative difficulty that can be encountered as a result of disturbances in water balance caused by diabetes insipidus. In the second patient, the diabetes insipidus could not have resulted from any lesion of the neurohypophysis. It could only have been caused by a lesion of the hypophyseal stalk or the hypothalamus. The fact that the diabetes insipidus cleared indicated that the lesion inducing the diabetes insipidus was in part, at least, a physiologic development involving the supraoptic and paraventricular nuclei.

The two cases just cited touch upon the problem of diabetes insipidus and the antidiuretic hormone (ADH). According to the work of Verney[12] and many others, ADH is formed and works physiologically in the following manner: in the anterior part of the hypothalamus are vascular osmoreceptors which respond to variations in osmotic concentration of the arterial blood. If the plasma osmolarity increases, from dehydration, for example, it is of importance to the individual to retain water. This is accomplished by the secretion of ADH by the cell bodies of neurones in the supraoptic and paraventricular nuclei. Apparently the ADH is transported by a granular carrier substance along the axons of nerve cell bodies in the supraoptic and paraventricular nuclei. Some of these axons terminate low in the hypothalamus and others in the hypophyseal stalk, but the majority terminate in the neurohypophysis. ADH thus could be found in the hypothalamus or stalk but is normally stored in the neurohypophysis and enters the blood supply of the latter under the proper stimulus. The hormone ultimately promotes absorption of osmotically free water in the distal renal tubules.

If there is a decrease in palsma osmolarity in the arterial blood bathing the osmoreceptors (hypoosmolarity), from overhydration, for example, a normal physiology responds by inhib-

Fig. 5. *(Case 5)* Pneumoencephalogram showing evidence of normal sella turcica. Arrow points to tumor encroaching on cisterna interpeduncularis.

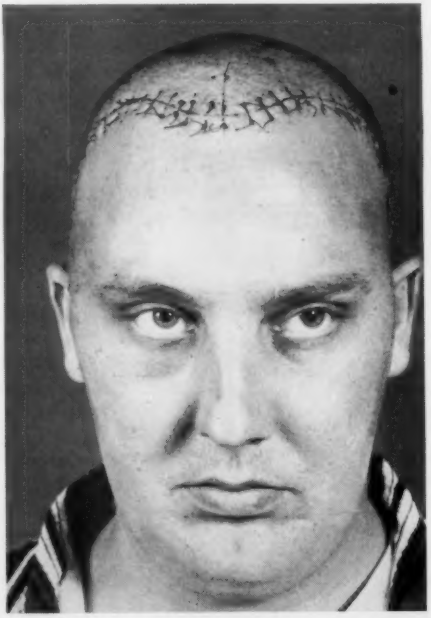

Fig. 6. *(Case 5)* Patient eight days postoperatively. Sparseness of beard is evident.

iting the formation of ADH, resulting in the promotion of water diuresis. If ADH formation were not inhibited in the presence of water loading, symptoms of water intoxication would be common.

As proved in in vivo and in vitro experiments, particularly by Hild,[13] the neurohypophysis does not secrete ADH. Ray[14] made application of this experimental work to human beings possible, when he showed that [1] total hypophysectomy does not necessarily result in diabetes insipidus and [2] the more closely to the hypophysis the hypophyseal stalk is cut, the less likely is diabetes insipidus to develop.

It is seen in case 4 that a boy weighing 45 lb. had a urine output of 5,785 cc. in a twenty-four-hour period. Calculated for a 140-lb. adult, this output would have amounted to approximately 18 liters of urine in twenty-four hours; this is about the maximum in diabetes insipidus and indicates that almost no ADH is being produced to act upon the distal renal tubules.

Case 5 was discharged from the hospital with diabetes insipidus that was destined to be transient. Pneumoencephalographic studies and operative findings suggested that the entire hypophysis was intact. The diabetes insipidus, then, must have been caused by a lesion in the hypothalamus which was, at least in part, reversible or physiologic. When this patient left the hospital twelve days postoperatively, he was given injections of 0.5 cc. of Pitressin tannate in oil every two days. Apparently, the diabetes insipidus cleared while he was taking Pitressin, and he continued, perhaps from habit, to take a good deal of water. Although inhibition of the formation of the patient's own ADH may have taken place because of hypoosmolarity of the blood, the patient's distal renal tubules resorbed too much water – because of iatrogenically administered ADH – and an almost fatal water intoxication resulted. Water intoxication probably would not have developed in a normal individual under the same circumstances, but this patient's control of his own water balance must have been in a rather uncertain state at the time. Injection of Pitressin on a symptomatic basis is what should have been advised in this case when the patient was discharged from the hospital.

DISCUSSION

Diagnosis of craniopharyngiomas, when the telltale midline suprasellar calcification is present, is usually easy to make in children. Of the 4 adults in this series, the diagnosis of craniopharyngioma was missed in 3 before operation and only suspected in the remaining patient. None of these lesions was calcified.

In the literature, incidence of roentgenographically demonstrable calcification in craniopharyngiomas is said to be between 50 and 90%. These statistics present a false picture, however, for certainly more than 50% of children and far less than 90% of adults with craniopharyngiomas show suprasellar calcification. From a study of the literature, it seems fair to say that above 80% of individuals under the age of 20 and fewer than 20% over the age of 40 who have craniopharyngiomas show suprasellar calcification on roentgenographic examination. At the same time, it is probably correct to say that something less than 20% of all craniopharyngiomas manifest themselves after the patient has passed the age of 40.

Since the majority of craniopharyngiomas are not calcified at the time when pituitary and suprasellar adenomas and suprasellar aneurysms appear clinically, lesions in the region of the sella are most difficult to differentiate, particularly in the presence of a normal sella turcica. In a nine-month period, the diagnosis of suprasellar meningioma was made by Cushing[15] 11 times, with 8 diagnostic errors as to the histology of the lesion. This was after Cushing had assembled the material for his classical paper (with Eisenhardt) on "Meningiomas Arising from the Tuberculum Sellae." Of the lesions, 2 proved to be uncalcified craniopharyngiomas. Enlargement of the sella turcica does not invariably accompany a pituitary adenoma. It was Cushing's belief that these suprasellar adenomas arose from *Anlagen* in the hypophyseal stalk or escaped through the diaphragma sellae without having previously expanded the sella.

It is interesting to observe that papilledema is almost never associated with craniopharyngiomas in individuals over 40 years of age. In 12 patients over age 40 operated upon at the University Hospital since 1925 for craniopharyngioma, none had papilledema. Of 63 patients under 40 operated upon during the same period, 28 (43%) had, or had had, papil-

ledema. One would almost suspect that there is some correlation between calcification and papilledema in craniopharyngiomas.

In an interesting article, Wertheimer and Corradi,[16] discuss 18 patients over 40 years of age with craniopharyngiomas upon whom they operated. The immediate operative mortality was 27%. In only a few cases, however, was cortisone used to prepare the patient for operation. In 9 patients, the results were good; 6 patients survived from six to eighteen years. It was believed that total excision of the tumor had been accomplished in only 1 patient.

Since the results of Wertheimer and Corradi are roughly comparable to mine, it may be that we have been too radical in operating upon adults with craniopharyngiomas. The surgeon must decompress the optic nerves and chiasm and relieve third ventricle obstruction, but it is probably a mistake for him to attempt to remove small, inaccessible bits of remaining tumor. This judgment, in my opinion, does not apply to younger people with greater life expectancy.

We have used x-ray therapy on only 2 patients and this use was inadvertent. In case 5, the tumor was suspected of being a suprasellar chromophobe adenoma, and a complete course of x-ray therapy was administered on the basis of this suspicion. A definite improvement in visual acuity appeared, and lasted for three months. When the symptoms returned, an operation was performed and a solid craniopharyngioma was removed from behind the chiasm. The second patient was also thought to have a suprasellar chromophobe adenoma. X-ray therapy had only been started when the patient went into coma and was operated upon in an emergency procedure.

In a report from the Mayo Clinic, Leddy and Marshall[17] felt that amelioration of symptoms could be attributed to roentgen therapy in 10 of 15 patients. It was their belief that irradiation probably inhibits the formation of cystic fluid by destroying the secretory power of the tumor cells. No cyst was present in patient 5, and, therefore, their theory did not apply. It is difficult to believe that therapeutic doses of x-ray can have any real effect on the well differentiated epithelial cells of craniopharyngiomas.

If a lesion in the region of the chiasm produces symptoms and a definite diagnosis of hypophyseal adenoma cannot be made with certainty, surgical exploration is preferred to temporizing with x-ray therapy.

SUMMARY

1. The craniopharyngiomas should be approached radically from a surgical point of view, and, in some incidences, total excision may prove possible.

2. Hyperthermia and circulatory collapse are uncommon postoperatively when the patient has been properly prepared with cortisone. If these conditions do develop, treatment should be on a physiologic basis.

3. Postoperative diabetes insipidus was absent in 5 patients, transient in 7, and has remained to date in 6.

4. After the patient has returned home, the relatives and family physician should be alerted to the fact that pituitary insufficiency and severe hypoglycemic reactions may develop even if clinical evidence of hypopituitarism and hypoadrenalism is lacking at the time of discharge.

5. If there is reasonable doubt as to the histology of a chiasmal lesion, one should ordinarily not temporize with x-ray therapy but should explore the sellar region surgically.

I wish to express my appreciation to Dr. Stefan S. Fajans of the Department of Medicine, Section of Endocrinology and Metabolism, and Dr. Rose H. Parker, Department of Medicine, for suggestions made while checking the manuscript.

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Annual Meeting
American Academy of Neurology

April 16-19, 1959

Statler Hilton Hotel, Los Angeles

Experiences with metastatic neoplasms involving the spinal cord

Kevin D. Barron, M.D., Asao Hirano, M.D., Shukuro Araki, M.D., and Robert D. Terry, M.D.

AN ANALYSIS is presented of 127 necropsied cases of symptomatic involvement of the spinal cord and cauda equina by metastatic neoplasms. Observations are made on the frequency of metastasis by different neoplasms, and the natural history of each type of metastasis is examined to indicate where important clinical differences exist in the mode of onset, progression, and response to treatment. The results of operation in 38 patients are described and criteria for operation are presented. Finally, pathogenesis is considered of spinal cord lesions accompanying metastatic neoplasms.

Frequency of metastasis from certain malignant extraspinal neoplasms. Table 1 indicates the frequency with which certain common types of malignant extraspinal tumors produce symptomatic metastasis to the spinal cord. The figures are based on material autopsied at this institution from 1950 to 1956. The true incidence may well be higher than indicated, since asymptomatic lesions might have been missed.

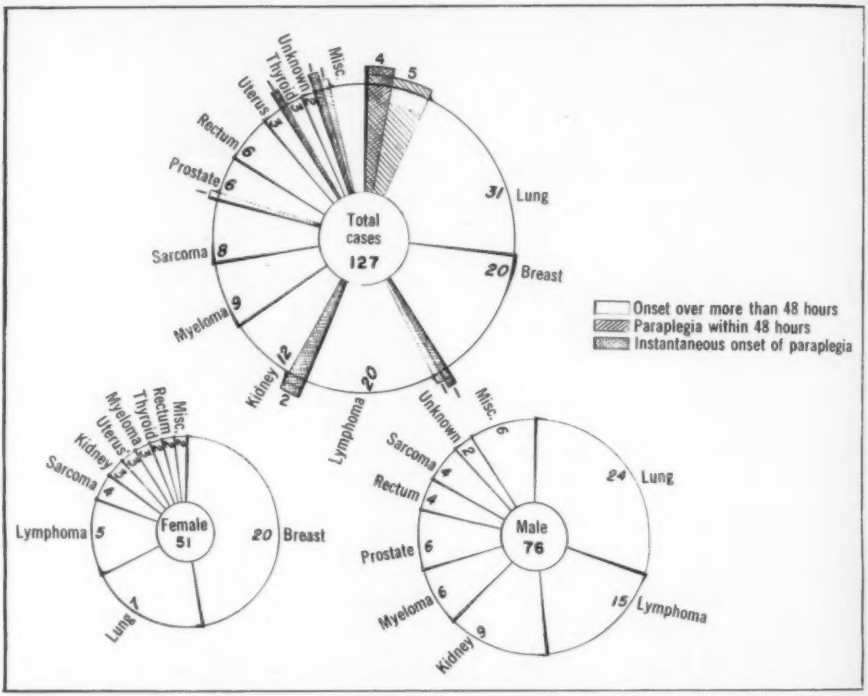
The frequency of spinal cord complications in Hodgkin's disease[1] may be higher than the percentage recorded in Table 1 under lymphoma. Although carcinoma of the stomach is one of the most common cancers and is the most frequent cause of meningeal carcinomatosis,[2] spinal epidural metastasis from this source would appear to be uncommon. The 126 cases of carcinomatous epidural metastasis included in the reports of Wilson and Rupp,[3] Neustaedter,[4] and Wolf[5] contain but 6 gastric carcinomas. In 85 consecutive stomach carcinomas proved at necropsy, we encountered only 1 instance of symptomatic epidural metastasis. In the case of carcinoma of the prostate, metastatic cord involvement is relatively frequent.[3,4] The large experience of Bumpus[6] indicating a low incidence — around 1% — of cord involvement in this tumor does not compare with ours, because estrogens and orchiectomy which may prolong life, thus providing opportunity for metastasis, were not then in use, and it is not clear how long his patients were followed or how often necropsy was performed. With regard to multiple myeloma, Clarke[7] concluded, after an extensive review of the literature, that cord involvement occurred at some time during the clinical course in 6% of patients.

Primary sites of epidural metastasis in a general autopsy series. Graph 1 depicts the incidence of primary neoplasms which gave rise to spinal cord involvement in 127 patients. In contrast to our experience, neither Neustaedter[4] nor Elsberg[8] mentioned carcinoma of the lung. Wilson and Rupp[3] reported 4 lung carcinomas among 53 tumors metastasizing to the spinal cord, but their series did not include any primary tumors of the breast. Wolf,[5] through reporting material which was largely surgical, recorded an experience more closely parallel to our own. The frequency with which lymphomas cause compression of the spinal cord is attested to by the many reports on the subject.[9–20]

Carcinoma of the kidney figures significantly in the series of Wilson and Rupp,[3] Neustaedter,[4] Wolf,[5] and Elsberg.[8] Of the 12 cases of renal carcinoma included in our statistics, 9 arose in the left kidney. Wohl[21] has commented on the tendency of carcinoma of the left kidney to metastatize to the spine and has suggested that this metastasis is related to venous drainage.

From the Henry and Lucy Moses Research Laboratories of the Laboratory Division, Montefiore Hospital, New York City.

Dr. Barron is a trainee of the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Bethesda, Md.



Graph 1. Incidence of neoplasms according to primary sites, sex distribution, and acuity of onset of paraplegia. The upper diagram indicates the rapidity of onset for each tumor type. The lower figures denote the sex distribution of the neoplasms. The miscellaneous category includes 1 case each of hepatoma, carcinoma of the ovary, lymphoepithelioma of the nasopharynx, malignant mixed tumor of the parotid gland, seminoma, anaplastic carcinoma of the pancreas, and malignant cutaneous melanoma.

CLINICAL PICTURE

The extramedullary (extradural) metastatic tumors of the spinal cord are distinguished clinically by acuity of onset and rapidity of progression. The course to maximal neurologic deficit is often measured in hours or days. Of the patients in this series, 30% were paraplegic* within a week. Paraplegia and incontinence developed overnight in 4 patients who had had a slowly progressive paraparesis. Acute exacerbations in a chronic course occurred in several other patients. In contrast, benign tumors progress to paraparesis in weeks or months. The symptoms of metastatic spinal tumors are almost invariably and inexorably progressive, while benign extramedullary neoplasms may have a remissive course,[22,23] though admittedly this is rare.

Paraplegia without cutaneous sensory loss is said to be common in metastatic cord lesions,[3,24] but, among many patients in the present series who presented a complete motor paralysis on admission or developed paraplegia while under observation, only 1 had normal cutaneous sensibility. Otherwise, paraplegia was invariably accompanied by loss or impairment of all forms of cutaneous sensation below the level of the lesion. Severe paraparesis did occur with relatively slight sensory loss, but, even then, hypalgesia of a segmental

*Paraplegia, as used in this paper, indicates total motor paralysis of the lower limbs. Paraparesis is defined as partial motor paralysis.

TABLE 1
MALIGNANT TUMORS AT AUTOPSY (1950-56)

Primary site	*Number of patients*	*Metastases to cord*	*Per cent*
Lung	225	11	4.9
Breast	93	6	6.5
Lymphoma*	86	4	4.6
Stomach	85	1	1.2
Rectum	45	3	7.0
Prostate	40	4	10.0
Kidney	40	3	8.0
Ovary	36	0	0
Multiple myeloma	21	3	14.0
Thyroid	17	1	6.0
Uterus	16	1	6.0

*Under this designation are included patients with Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, and leukemia.

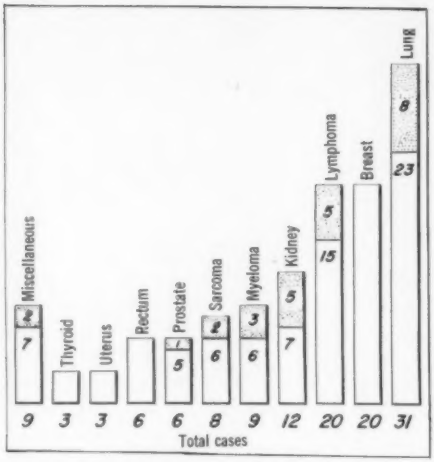
distribution could very commonly be demonstrated, and often position, touch, or vibratory sense was impaired or lost. The degree of sensory dysfunction observed contrasted with Tarlov's experimental observations[25] on artificial compression of the dog spinal cord, where serious motor deficit was frequently produced without affecting the response to pinprick.

A well-recognized feature of extramedullary neoplasms is the presence of a sensory level several segments below the site of the cord lesion. This discrepancy is usually explained on the basis of the known lamellation of the fibers in the spinothalamic tracts. A false sensory level was not an uncommon finding in this series. In several instances, extramedullary lesions at the mid and upper thoracic segments of the cord were associated with sacral sparing. This phenomenon is commonly considered pathognomonic of intramedullary cord disease.

Back and/or radicular pain preceded evidence of spinal cord or cauda equina dysfunction in 82% of the patients. Radicular pain referable to the extremities was common in lesions of the cervical and lumbosacral spine and was usually accompanied by local pain in the back. Lesions of the thoracic spine were particularly likely to give rise to pain and tenderness more or less localized to the involved vertebrae. Less frequently, thoracic spine metastasis caused radicular pain of a girdle character. Local tenderness and girdle pain sometimes accurately indicated the site of subsequent compression. The pain in the back was often dull, aching, and continuous. Pain was sometimes specifically described as worse at night and aggravated by movement. It was uniformly severe and caused the patient to seek advice from his physician who, because of the nonspecific nature of the complaint, was prone to attribute symptoms to arthritis or neurosis.

A few patients manifested atypical syndromes; 1 presented a picture of rapidly ascending "myelitis" and died nineteen days after onset. Autopsy disclosed a bronchogenic carcinoma with intramedullary metastasis throughout the length of the cord. A patient with a malignant mixed tumor of the parotid gland had a persistent Brown-Séquard syndrome. The metastasis was extramedullary but practically encircled the cord. In the single instance of meningeal carcinomatosis in this series, the presenting signs and symptoms suggested a peripheral neuropathy.

Signs and symptoms as related to the primary tumor. Graphs 1, 2, and 3 illustrate certain important distinctions in the clinical picture presented by metastasis from different primary tumors. Data on the rapidity of development of paraplegia are summarized in Graph 1. Paraplegia, so sudden in onset as to be apparently instantaneous, and paraplegia developing in less than forty-eight hours from the first symptoms of cord disease were particularly likely to occur in bronchogenic carcinoma. In carcinoma of the breast, the clinical course was always slower. Instantane-



Graph 2. Metastasizing neoplasms whose first manifestation was that of spinal cord disease. The stippled areas indicate cases in which physical examination, chest roentgenograms, and the usual laboratory procedures failed to reveal a primary neoplasm elsewhere prior to operation or autopsy.

ous onset or rapid progression to complete motor paralysis of the lower limbs occurred with other tumors, particularly lymphomas and carcinomas of the kidney. Instantaneous onset of paraplegia has been reported in Hodgkin's disease,[1] multiple myeloma,[26] and a case of probable carcinoma of the prostate.[27]

Graph 2 shows that bronchogenic carcinoma, lymphoma (including Hodgkin's granuloma), carcinoma of the kidney, and multiple myeloma frequently presented signs of spinal cord involvement before the primary neoplasm was diagnosed. In contrast, the diagnosis of carcinoma of the breast was already established when cord symptoms secondary to this neoplasm appeared.

In Graph 3, the behavior of the various primary neoplasms with regard to back and radicular pain is summarized. Not uncommonly, patients with bronchogenic carcinoma and malignant lymphoma developed spinal cord disease without a history of back or radicular pain. By contrast, cord involvement by carcinoma of the breast was almost invariably preceded by these symptoms. Further, the median duration of pain in carcinoma of the breast was more than twice that of lymphoma and bronchogenic carcinoma. The number of patients with multiple myeloma and carcinoma of the rectum was relatively small, but their behavior regarding pain paralleled that in carcinoma of the breast. The behavior of carcinoma of the kidney resembled that of malignant lymphoma and bronchogenic carcinoma.

As to the nature of the symptoms and signs of cord disease once developed, little difference was found among various tumor types, except that a flaccid, areflexic paraplegia often occurred in bronchogenic carcinoma and was apt to be associated with notable muscular wasting. The rapidity of progression of the cord disease in lung carcinoma may explain the high incidence of flaccid paraplegia and the fact that we failed to observe spastic paraplegia with this neoplasm.

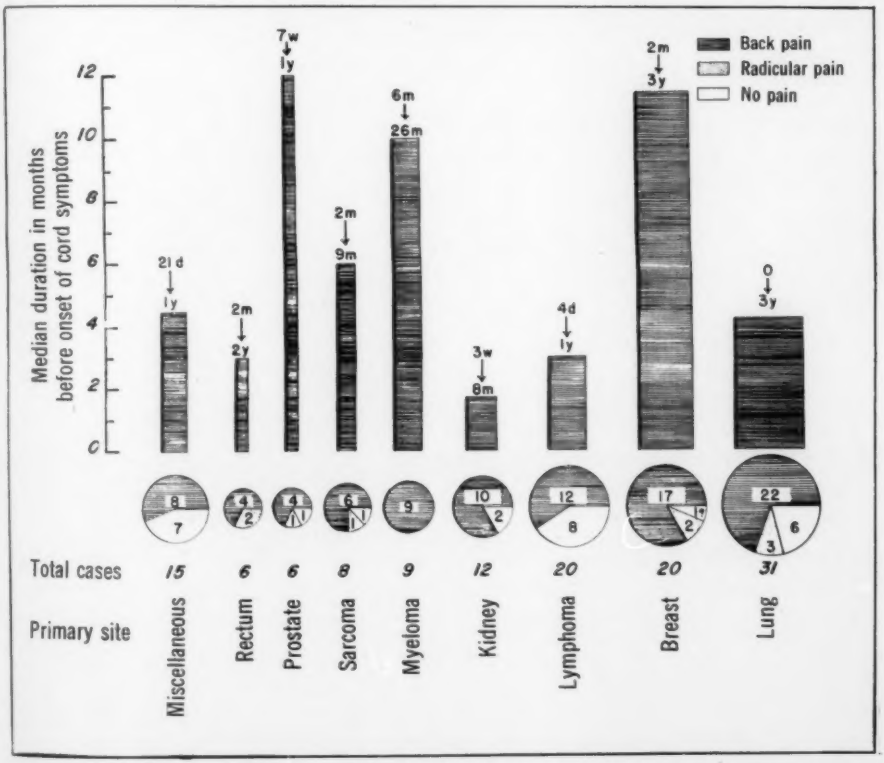
Signs and symptoms as related to the location of the lesion. Prolonged pain was typical of the 14 patients with metastasis to the cervical cord. The pain began in the neck but radiated into one shoulder or down one arm into the hand and preceded cord involvement by seven months to two years. Weakness and atrophy in muscle groups accompanied the pain which eventually affected the other upper extremity. Plain roentgenograms of the cervical spine usually demonstrated a lesion at this time. Symptoms referable to the lower extremities or to the sphincters were an index of compromise of the cord. Once they appeared, progression to paraplegia and incontinence was usually complete within one week. In 1 patient with cervical cord metastasis from a bronchogenic carcinoma, symptoms progressed to a quadriplegia in less than twenty-four hours without a prior history of pain.

The patients with metastasis to the thoracic segments of the spinal cord presented a different picture. In 53 of these patients, the histories available were particularly complete and were selected for meticulous analysis. Pain was not experienced by 37%. Pain, when present, was felt in the back and rarely radiated. The average duration of pain prior to onset of cord compression was six months. Progression to a complete transverse lesion of the cord as manifested by paraplegia, incontinence, and sensory loss below the level of the lesion was particularly frequent. Of patients

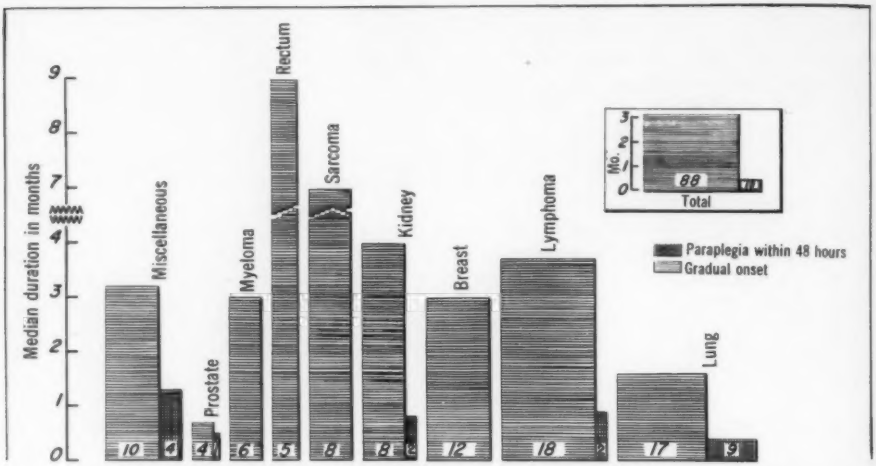
with lesions of the thoracic cord segments, 12 were paraplegic within twenty-four hours of onset of symptoms of cord disease; 4 were paraplegic within forty-eight hours; and 15 others within one week. Motor, sensory, and sphincteric symptoms could not always be separated in sequence of appearance. Weakness of the lower limbs was the most common initial complaint, but, occasionally, incontinence was the very first symptom and in 1 patient was the only symptom for several weeks. Paresthesias were also a presenting symptom in some cases.

Tumors in the region of the conus medullaris were sometimes separable from cauda equina lesions on the basis of rapid progression of symptoms and signs, absence of radicular pain, and constant presence of sphincter disturbance early in the course of the disease.

The syndrome presented by lesions of the cauda equina was usually characteristic. Severe pain in the low back with radiation into one or both legs was the earliest symptom and sometimes persisted for many months. Some patients complained of paresthesias; objective impairment of sensation was sometimes absent. Weakness was insidious and commonly associated with muscular atrophy and diminution or loss of reflexes. In 1 patient no objective motor weakness occurred. Roentgenograms of the lumbosacral spine usually demonstrated osseous metastasis early in the course.



Graph 3. Incidence and duration of back and radicular pain prior to cord symptoms. The shaded areas indicate the presence of back pain, often with radicular pain. The stippled areas denote radicular pain alone. A single case of carcinoma of the breast is questioned because of an inadequate history on this point.



. Graph 4. Survival after onset of cord symptoms

Attempts proved fruitless to analyze the clinical signs and symptoms presented by our patients by relating the quadrant of the cord to the extradural mass. In many patients, the tumor practically encircled the cord. In patients in whom tumor was more or less confined to one plane or quadrant, no consistency was found in the accompanying clinical syndrome. McAlhany and Netsky[28] were also unable to detect any pattern in the clinical picture presented by an extramedullary neoplasm which would allow the mass to be placed with any assurance anteriorly, laterally, or posteriorly to the cord.

Herpes zoster. The first reference in the English literature to herpes zoster in malignant disease of the spine was by Head and Campbell.[29] This complication has been reported in Hodgkin's disease,[1,10,19,30] lymphosarcoma,[12] multiple myeloma,[26] and carcinoma.[31,32] Goldman[1] was impressed by the occurrence of zoster at spinal levels which were subsequently the site of cord compression. He suggested that patients with Hodgkin's disease who developed herpes zoster be given prophylactic radiotherapy to the appropriate area of the spine. However, zoster has been frequently observed in lymphoma patients who did not subsequently develop cord disease.[19,30]

In the present series, 7 patients presented an eruption typical of herpes zoster in the course of their illness. In each, the zoster was at the level of cord compression. The primary tumors were Hodgkin's disease (3), bronchogenic carcinoma (2), carcinoma of the thyroid (1), and leiomyosarcoma of the uterus (1). The eruption was always unilateral and limited to 1 or 2 dermatomes. In 1 patient, the eruption had a T12, L1 distribution, but, in the others, zoster was confined to thoracic segments. After the appearance of a thoracic herpes, 1 patient had a generalized eruption similar to that seen in varicella.

Of the patients with Hodgkin's disease, 2 developed a spinal cord lesion at the site of the zoster about 1 year later. In 3 patients, herpetic rash accompanied the spinal cord syndrome, and in 2, rash followed the syndrome in two months. The posterior roots were examined in 1 patient and were found to be infiltrated by tumor cells. Merritt[33] believes that herpes zoster in cancer patients is the result of activation of a latent virus by tumor involvement of posterior root ganglions.

Survival. Graph 4 indicates that the median length of survival of the patients with cord compression was considerably less in primary carcinoma of the lung than in malignant lymphoma or in carcinoma of the breast – this despite the fact that cord compression in car-

cinoma of the breast developed late in the course of the disease. The survival time in carcinoma of the kidney lay between that of bronchogenic carcinoma and lymphoma. Patients with progression to paraplegia in less than forty-eight hours had a particularly short life expectancy. Multiple myeloma and carcinoma of the rectum resembled carcinoma of the breast regarding survival time, but the total number of cases was small. The patients usually died from a combination of cachexia, infected and draining decubiti, bronchopneumonia, and urinary tract infection. In 2 patients, decubiti eroded the sacrum, exposed the subarachnoid space, and caused a fatal, purulent meningitis.

LUMBAR PUNCTURE AND SPINAL FLUID ANALYSIS

Lumbar puncture was performed in 72 patients. In 45, adequate information was available concerning spinal fluid manometrics when maximal neurologic deficit developed. In 31 patients a complete manometric block was demonstrated. Partial block was reported in 4. In 10, assurance was found that no manometric block existed, and, in these patients, the site of compression ranged from the low cervical area to the cauda equina.

It is well known[34,35] that patients with extramedullary lesions may have open manometrics on lumbar puncture. Poppen[36] showed that if a communication equal in diameter to the bore of the needle exists at the site of the lesion, no manometric block will be demonstrable. The statement that open manometrics indicate an acute, vascular[24] lesion of the cord is contradicted by our patients with open manometrics in which the duration of cord symptoms and signs from onset to paraplegia varied from two days to several months.

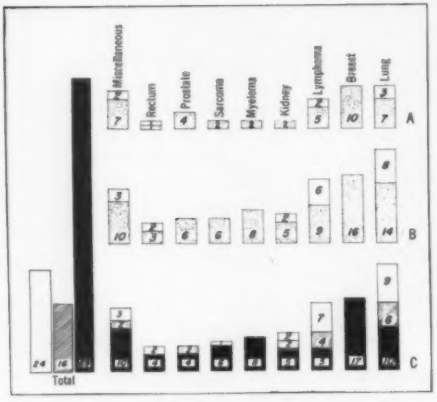
Spinal fluid total protein determinations were done in 39 patients. The level of the spinal lesion and the type of tumor could not be correlated with the degree of elevation of spinal fluid protein except in lesions of the cauda equina, wherein the highest protein values were obtained. In 1 such patient, a value "greater than 2,000 mg. per cent" was recorded, and, in another, the xanthochromic fluid clotted on standing. The lowest protein level reported in the case of a complete manometric block was 48 mg. per cent. Otherwise protein values in these circumstances ranged from 82 to 822 mg. per cent. In patients with partial manometric block, proteins ranged from 33 to 500 mg. per cent. Xanthochromia was not well correlated with the protein level, but objective methods of determining the former factor were not used.

The spinal fluid glucose and cell count were usually determined. Only once was there pleocytosis. This patient, who had carcinomatosis of the meninges, had a cell count of 24 lymphocytes and 6 polymorphonuclear leukocytes. Pleocytosis is not uncommon in this condition. Spinal fluid glucose was uniformly normal when estimated but was not determined in a single patient with meningeal carcinomatosis.

Never in this series was there a change in the neurologic findings or a worsening of the patient's condition which could be ascribed to lumbar puncture. Sudden progression of the patient's disability following lumbar puncture has been reported in primary extramedullary spinal cord tumors[24,37] and is a generally recognized complication of the procedure. Progression of the patient's signs following spinal tap has also been noted in multiple myeloma and lymphosarcoma.[7,17,26,38]

MYELOGRAPHY

The most important observation disclosed by review of the results of myelography was that injection of the oily medium by the lumbar route sometimes failed as an adequate guide to operation. Metastatic epidural tumors are often distributed over a considerable extent in the longitudinal plane. The lumbar myelogram reveals only the caudal limit of the tumor. The site of major compression may be above the level of block demonstrated following lumbar injection. Clinical findings may be misleading because the sensory level detected on examination may be several segments below the zone of actual compression. Tumor anterior to the cord and cephalad to an operative site indicated by lumbar myelography may elude the neurosurgeon. For these reasons, we recommend that lumbar myelography be more often combined with Pantopaque instillation into the cisterna magna. The combined procedure is particularly important if the level of spinal pain or tenderness or the presence of



Graph 5. Radiographic evidence of vertebral metastasis. *A*. The stippled areas indicate those patients in whom bone lesions were visualized at a time when pain was the only symptom. *B*. The stippling denotes the incidence of radiologic lesions at the onset of paraparesis or paraplegia. *C*. Incidence of radiologic lesions during the entire course of the disease. The black areas represent multiple lesions; the shaded areas denote single lesions. White areas indicate those patients without demonstrable bony lesions.

radicular pain in the upper limbs suggests a lesion above the level of obstruction detected by lumbar myelography. Myelography by the lumbar route did not convey adequate information or was positively misleading concerning the extent of the neoplasm in 7 patients. In consequence, the laminectomies in these patients were not extended to the cephalad limits of the tumor and this may account for the lack of postoperative improvement.

Myelograms were performed on 25 patients, and all but 5 had laminectomy. In only 1 patient was a myelogram normal. Myelograms in the remaining patients demonstrated a complete block to the flow of the oily medium with the exception of 1 patient with cauda equina compression. The configuration of the obstruction was frequently described as strongly suggestive of an extradural lesion. Of patients with myelographic block above the site of needle puncture, 1 had had no demonstrable manometric block. The obstruction to the flow of oil in this patient was at D10. A manometric block may not be demonstrable in the presence of complete obstruction to the passage of the radiopaque medium.[34,35]

The over-all value of myelography is amply illustrated by our case material. Apart from information as to site, myelography often indicates the character of the lesion – extradural and probably malignant. Plain roentgenograms of the spine may not supply this information for several reasons: first, they may be normal, as was true in 9 of our patients who had operation; second, abnormalities may be confused with Paget's disease or senile osteoporosis; and third, vertebral metastasis seen on the plain film may be distant from the site of cord compression.

ROENTGENOGRAMS OF THE SPINE

The radiologic appearance of the spine in metastatic tumors differs sharply from that accompanying primary extramedullary tumors. The latter present pedicular erosion and widening of the interpedicular space. Metastatic tumors show destruction and erosion of parts of the vertebrae often sufficient to produce collapse. Sometimes metastasis to the vertebrae gives an appearance of increased density – osteoblastic metastasis. This appearance is particularly seen in carcinoma of the prostate, although scirrhous carcinoma of the breast, Hodgkin's granuloma, and other tumors may produce a similar appearance. Actually, bone metastasis usually produces mixed lytic and blastic changes. A further characteristic of metastatic spinal tumor is the occasional presence of a soft tissue mass in the paraspinal tissues.

Graph 5 illustrates the results of roentgenography of the spine at different stages in the clinical course. The plain spine roentgenograms in 83% of patients complaining only of back or radicular pain revealed abnormality which was diagnostic or suggestive of metastatic neoplasm. At this stage, abnormal spine films were the invariable rule in carcinoma of the breast in contrast to some carcinomas of the lung and lymphomas. Even in the later stages of cord involvement, certain patients had no demonstrable bone destruction. The results of roentgenographic examination of the vertebral column in multiple myeloma and carcinoma of the prostate paralleled those in carcinoma of the breast. These 3 tumors exhibited abnormalities of the plain roentgenograms

of the spine at all stages in the course from pain to paraplegia, and this fact was of differential diagnostic importance. Carcinoma of the kidney resembled bronchogenic carcinoma and malignant lymphoma. Of patients in the whole series, 22% had normal plain spine films at a time when there was definite clinical evidence of a lesion of the spinal cord or cauda equina. Many of these demonstrated histologic evidence of metastasis to the bodies of the vertebrae at autopsy. The occurrence of large metastatic deposits within the vertebrae in the absence of radiologic abnormality is not uncommon and was discussed by Epstein.[39]

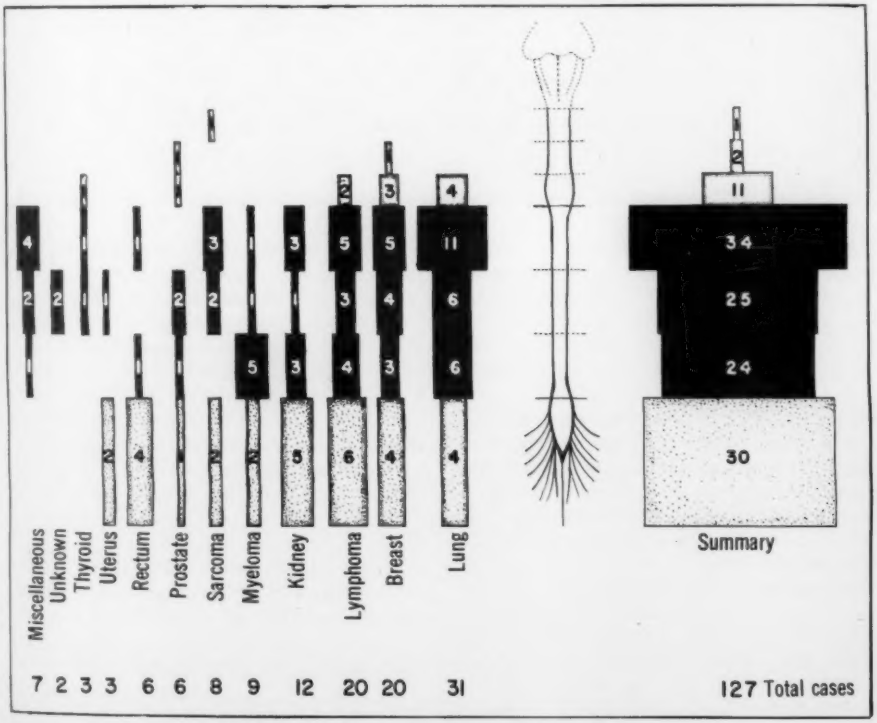
Graph 5 also shows that in carcinoma of the breast with cord involvement, as well as in multiple myeloma, several vertebrae were invariably involved. This finding represented another difference between these tumors and carcinoma of the lung, malignant lymphoma, and carcinoma of the kidney.

Often the abnormality seen in the roentgenograms of the spinal column corresponded to the site of neural involvement. However, in 8 patients, the radiologic lesion was distant from the site of the cord lesion. In 7 patients, the vertebrae were too diffusely involved to be of any assistance in localization.

Although any tumor may metastasize to any part of the spine, some malignant neoplasms have sites of predilection. Carcinomas of the lung in this series metastasized most commonly to the dorsal vertebrae; carcinomas of the kidney, prostate, and rectum to the lumbosacral vertebrae.

TREATMENT OF SPINAL CORD METASTASIS

The approach to the treatment of metastatic carcinoma of the spinal cord has long been a nihilistic one. Elsberg[24] stated, "In proved metastatic carcinoma of the vertebrae, there is very rarely, if ever, any justification for the



Graph 6. Level of maximum metastatic involvement

attempted removal of the malignant disease." Rasmussen and Kernohan[40] and Shenkin, Horn, and Grant[41] were of the same opinion and also disapproved of surgical intervention in cord compression by multiple myeloma. Actually, 2 of the patients with multiple myeloma operated upon by Shenkin and his coworkers appear, by their own accounts, to have obtained substantial improvement; surgical relief of spinal cord symptoms accompanying this tumor has been described elsewhere.[7,26,42–44] A patient with myeloma[45] survived fifteen years following laminectomy and radiotherapy. Recently, there have been accounts[38,46–48] of beneficial results from laminectomy in cases of metastatic carcinoma. In contrast to the former attitude toward carcinoma and myeloma of the epidural space, optimistic reports of surgical treatment of spinal cord involvement by Hodgkin's disease and lymphosarcoma have long been current[15–17,19] and have recently been confirmed.[20,47] Unquestionably, laminectomy is the most useful tool in the treatment of metastatic spinal neoplasms. However, most reports dealing with tumors of the lymphoma group and multiple myeloma have stressed the importance of combining surgical therapy with radiotherapy.

Favorable response of cord symptoms and signs in Hodgkin's disease and lymphosarcoma to radiotherapy alone has been reported.[1,9,12,19] Blakeslee's patient was paraplegic, incontinent, and anesthetic below the level of the lesion but became ambulatory following radiotherapy; improvement was maintained over a two-year follow-up. One of our patients with a malignant vascular tumor made a remarkable recovery which was probably related to radiotherapy as much as to laminectomy.

The literature also contains accounts of the use of chemotherapy for certain patients with metastatic cord neoplasms. In 1949, Edelman[49] reported striking recovery from paraplegia secondary to carcinoma of the prostate by administration of stilbestrol to a patient who had not had prior therapy by orchiectomy or estrogenic hormones. No evidence is found that urethane or stilbamidine therapy alone is of value in multiple myeloma with cord involvement, but several patients who have benefited by laminectomy have received these drugs.[7] Conceivably, nitrogen mustard and related compounds might be of value in Hodgkin's disease with spinal cord compression, but we have encountered no specific reports to this effect and our own experience with 2 patients has been disappointing.* Mullan and Evans[38] reported marked benefit from the use of radioactive iodine in a case of thyroid carcinoma with cord compression.

Results and prognostic factors in surgical treatment. In this series, 38 patients had laminectomy; 11 improved postoperatively; 7 grew worse – except in 2, worsening was interpreted as the natural progression of the disease.

Both exceptions were found on recovery from the anesthetic to have signs of persistent, complete, transverse lesion of the spinal cord. The median survival of the operated group computed from onset of spinal cord symptoms was 105 days, a value little different from the median survival of the whole series. However, the mean or average survival in the operated group was 9.2 months, a figure slightly more than twice the mean survival of the group as a whole. Obvious bias is found in this latter computation, but it reflects the occasional long-term survivals following laminectomy. In the specific instance of carcinoma of the lung, median and mean survivals in the operated cases – 32 and 58 days, respectively – were not significantly different from the nonoperated cases.

The relief of pain which often followed laminectomy was presumably the result of removal of tumor and decompression of the posterior nerve roots. In several patients, posterior rhizotomies were done. A patient who had a bilateral posterior rhizotomy from T-3 through T-6 developed a complete transverse lesion of the cord immediately following the procedure, presumably as a result of compromise of the blood supply.

Three patients with cauda equina compression were treated by laminectomy and removal of extradural tumor. The patients survived two to six months. However, 1 had striking relief of pain postoperatively and return of strength in paretic muscles.

The recent reports of Tarlov on experimental compression of the spinal cord of the dog[25,50,51]

*A recent report by Williams and associates[39] concerns the successful management of such patients by combined chemo- and radiotherapy.

TABLE 2
SURGICAL RESULTS AS A FUNCTION OF RAPIDITY OF ONSET OF PARAPLEGIA

Development of paraplegia in days	*Total number*	*No improvement*	*Slight improvement*	*Marked improvement*
0 to 3	4	4	0	0
4 to 7	4	2	0	2
8 to 14	3	2	1	0
15 to 30	3	3	0	0
31 to 48	1	1	0	0

TABLE 3
SURGICAL RESULTS AS A FUNCTION OF DURATION OF SYMPTOMS

Duration from first symptom to operation (days)	*Total number*	*No improvement*	*Slight improvement*	*Marked improvement*
0 to 7	15	11	2	2
8 to 14	5	3	2	0
15 to 30	7	6	0	1
31 to 48	8	5	0	3

TABLE 4
SURGICAL RESULTS AS A FUNCTION OF PREOPERATIVE DURATION OF PARAPLEGIA

Length of time paraplegia present before surgery	*Total number*	*No improvement*	*Slight improvement*	*Marked improvement*
0 to 7	9	8	1	0
8 to 14	4	3	0	1
15 to 30	2	1	0	1

and on his clinical experiences in human spinal cord compression[47] led us to analyze (Tables 2-4) our surgical data according to the acuity of onset of spinal cord symptoms, their duration prior to surgery, and the degree of sensory function remaining below the level of the lesion. Particular reference was made to the presence or absence of paraplegia. The 6 patients listed as showing marked postoperative improvement had return of motor, sensory, and sphincteric function. Patients showing slight improvement had some return of function in one or all of these modalities, but recovery was minimal, short-lived, and without effect on the course of disease.

Table 2 suggests a poorer prognosis for those patients whose paraplegia developed in less than three days. Tables 3 and 4 show that a prolonged period between onset of symptoms or development of paraplegia and the date of operation did not preclude beneficial results.

It may be significant that all the cases described as very much improved had some preservation of sensation below the level of the lesion prior to operation. Of the 2 previously paraplegic patients who were much improved by operation, 1 manifested a sensory level 6 segments below the level of the lesion, and the other had some preservation of sensation in the lumbosacral segments. Tarlov[47] has commented upon the favorable prognostic significance of preservation of sensory function with complete motor paralysis. Mullan and Evans,[38] however, have reported 1 patient with a complete transverse lesion of two months' duration that was relieved by operation.

Table 5 indicates the results achieved by operation on each type of primary tumor and demonstrates that carcinoma of the lung had a uniformly unfavorable prognosis. That patients with a spastic paraplegia have a better prognosis after surgery than patients who are flaccid and areflexic has been previously noted.[37,52] In this series, both the patients who regained function following paraplegia

TABLE 5
SURGICAL RESULTS AS A FUNCTION OF THE PRIMARY NEOPLASM

Primary	*Number operated*	*Number improved*
Carcinoma of lung	9	0
Lymphoma	9	4
Carcinoma of kidney	4	2
Multiple myeloma	3	1
Sarcoma	4	2
Carcinoma of breast	2	1
Carcinoma of thyroid	1	1
Carcinoma, unknown origin	2	0
Carcinoma of liver, pancreas, adrenal	3	0
Lymphoepithelioma	1	0
	38*	11(29%)

*This total includes 3 patients with cauda equina compression.

had been spastic. None of 8 patients with flaccid, areflexic paraplegia had postoperative improvement. However, a patient who had flaccid paraplegia and areflexia secondary to multiple myeloma, recovered following operation and lived seven years.[44]

Indications for operation. Patients who, because of widespread metastasis, were emaciated, anemic, and otherwise in unsatisfactory general condition, were poor candidates for surgery and were not operated upon in this series, with few exceptions. However, widespread involvement of bone by multiple myeloma or carcinoma of the breast was compatible with satisfactory general condition and long survival and was not a contraindication.

The aim of laminectomy is not limited to excision of the metastatic tumor, for, in the course of operation, a portion of the rigid wall of the spinal canal is removed. This removal will be beneficial whether the cord is compressed by extradural tumor, by edema, or by fracture and angulation of the spine. At least 1 patient in this series was significantly improved by a decompressive laminectomy without removal of any intraspinal tumor.

In recommending laminectomy, one is not necessarily seeking to restore the patient to full activity, although this will occasionally be the gratifying result. The relief of pain, the restoration of sphincteric control, the return of power to the patient's limbs and trunk so that he can at least turn himself in bed may be the sole objectives. In short, laminectomy is justified if it makes the patient more comfortable and lightens the nursing problem during the last months of life.

Findings at exploration. At laminectomy, extradural tumor was usually found and, at least in part, eradicated. On 4 occasions, the surgeon did not find tumor within the spinal canal, although tumor was present at autopsy. Of these patients, 1 had an intramedullary lesion. In another, the tumor was anterior and lateral to the cord. On several occasions, passage of a rubber catheter above and below the operative field was specifically stated to have met no obstruction, but, at autopsy, the tumor was found to extend beyond operation site anterior and lateral to the cord.

In 2 patients in whom the surgeon described severe forward angulation of a pulseless cord in association with vertebral collapse, tumor was not discerned within the vertebral canal, although epidural tumor was present at autopsy performed fifteen days and thirty-eight days after operation. In several patients with angulation of a nonpulsating cord in the presence of vertebral collapse, the neurosurgeon felt that the amount of epidural tumor was not sufficient to cause cord compression.

In 4 patients, tumor was not found within the spinal canal at autopsy, although metastatic tumor had been removed at operation. This was true of 1 patient who survived more than eight years postoperatively. A patient with a carcinoma of the breast showed no postoperative improvement, although the offending ex-

tradural tumor appeared to have been completely removed. Possibly, in the 4 patients mentioned, more careful examination of the spinal canal and dura would have shown residual tumor.

CASE HISTORIES OF PATIENTS IMPROVING AFTER LAMINECTOMY

Case 1. A 52-year-old man with multiple myeloma developed a severe paraparesis in one week. After laminectomy and 3,000 r of radiotherapy for metastasis to the lower thoracic spine, motor, sensory, and sphincteric function completely returned. The patient survived eight years and eight months. Symptoms of cord compression did not recur.

Case 2. A 37-year-old woman with metastasis to the upper dorsal spine from a malignant hemangioblastoma developed a spastic paraplegia seven days after onset of signs of cord compression. Following laminectomy with apparent total removal of the extradural metastasis, only slight recovery occurred in five months. Radiotherapy of 3,000 r was then given; function returned rapidly and the patient became ambulant. She remained well for more than two years. Death was caused by cerebral metastasis.

Case 3. A 58-year-old woman who had had radical mastectomy for carcinoma of the breast became paraplegic and doubly incontinent in five to seven days. Paraplegia was accompanied by spasticity with flexor spasms and was present for twenty-six days prior to middorsal laminectomy. Postoperatively, she received 3,000 r of radiotherapy. Strength, sensation, and sphincter control returned to normal. Death resulted from widespread bony metastasis and pancytopenia three years and six months after laminectomy. Neurologic symptoms did not recur.

Case 4. A 62-year-old woman with known Hodgkin's granuloma had a slowly progressive paraparesis for eight days prior to laminectomy from D9 to D12. Tumor was not found at operation, but function returned strikingly before death from pulmonary embolism on the thirty-eighth postoperative day. Autopsy disclosed metastatic neoplasm anterior to the cord at the operative site.

Case 5. Severe paraparesis developed in less than twenty-four hours in a 32-year-old woman with thyroid carcinoma. Metastatic epidural tumor was excised at the level of vertebrae D4 to D6. Motor, sensory, and sphincteric function returned to normal, but the patient died nine months later from widespread metastasis.

Case 6. A 65-year-old man with carcinoma of the kidney had a severe paraparesis for six weeks before removal of an epidural metastasis at L1. Following operation and 5,000 r of radiotherapy, he became partly ambulatory and sensory and sphincteric function returned to normal. He remained improved for two years but died after recurrence of symptoms of cord compression.

PATHOLOGIC FINDINGS

Microscopic examination of this series of spinal cords has evoked more questions than answers. Histology varied significantly among clinically similar cases; it soon became apparent that a consistent system of clinicopathologic correlation would be impossible. A few positive generalizations can, however, be stated. Most important is the observation that the gray matter is often well preserved morphologically in comparison with myelinated tissue. Second, the pathologic alterations may be minimal despite severe and long-standing clinical disease.

In the majority of patients, malacia of the myelinated areas was a prominent feature at the level of the metastatic mass. Although the white matter was severely degenerated, the neurons usually showed only slight changes — such as slight cytoplasmic swelling and chromatolysis of the Nissl substance. Involvement of the gray matter by the malacic process was rare.

The histologic picture of spinal cord malacia associated with contiguous neoplasm was usually quite different from cerebral encephalomalacia or myelomalacia due to arterial occlusion. In the latter, chromophilia is promptly lost in the neurons, and, soon after, a similar fading of the glial processes, axis cylinders, and myelin sheaths occurs. Cell bodies, nuclei, and processes quickly lose their sharp outlines. In the compressed cord, the glial fibers and nuclei retained their bright

Fig. 1. Edematous malacia occupies most of the anterior funiculus. A small infarct-like lesion is noted near the anterior sulcus. (Hematoxylin and eosin × 50)

staining characteristics but were pushed apart, disorganized, and thinned out by enlarged extracellular spaces. These results were produced not merely by edema or even by demyelination, but by an actual loss of stromal elements. This picture was seen not only where the cord was visibly compressed, but also in those patients in whom the shape of the cord was unaltered by the adjacent tumor (Fig. 1). Malacia of this type was found in all of our clinical groups. Whether the paraplegia developed rapidly or slowly, whether the subsequent course was short or long, this was the kind of cord lesion often found at the level of the metastasis.

Occasionally accompanying this edematous type of malacia were small, sharply outlined focal infarcts resembling the classic lesions produced by arterial occlusion. These infarcts were distributed irregularly, often deep within the areas of edematous malacia.

The distribution of the edematous type of malacia was usually quadrantic and did not conform to the arterial supply or to the venous drainage. The arterial walls were not remarkable. Vascular occlusions were found only in a very few instances and then in the vessels accompanying the nerve roots through the intervertebral foramens. These few occlusions were caused by tumor emboli. The small veins were often congested.

Below the site of the cord lesion, the pyramidal tracts became Marchi positive within a few days. Spielmeyer and Kultschitzky stains for myelin and Sudan preparations for fat revealed degeneration several days later. This descending degeneration proceeded more slowly than did the ascending demyelination in the dorsal columns above the cord lesion. Degeneration of the ascending spinocerebellar tracts was relatively inconsistent. In several patients, even those with long-standing paraplegia with total sensory loss, these fasciculi did not demonstrate free fat or loss of myelin.

Metastasis to the substance of the spinal cord was as rare in this series as in those previously reported.[3,53–55] The present group of 127 patients included only 2 with intramedullary metastasis. In both, the primary tumor was a bronchogenic carcinoma. In 1, a single 7 mm. tumor mass was found in the substance of the lumbar spinal cord; in the other, numerous, small intramedullary metastases centered about tumor emboli and extensive necrosis was found in the thoracic, lumbar, and sacral segments.

DISCUSSION

Of the 19 patients with cord compression reported by McAlhany and Netsky[28] 14 are included in this series. Our findings are in agreement with their conclusions with regard to the relative sparing of the gray matter and of the anterior white columns. This is only relative, however, in that many patients did reveal moderate edematous malacia of the anterior white matter. Furthermore, slight loss of anterior horn cells and shrinkage or swelling with chromatolysis of the remaining neurons were common.

The significance of the dentate ligament in spinal cord compression as presented by Kahn[56] was disputed by McAlhany and Netsky. Again our conclusions are in accord with the latter authors, since we, too, have noted the sparing of the anterior columns — even in the presence of anteriorly placed tumors.

Wilson and Rupp[3] stated that extensive myelomalacia was found in every patient in whom clinical symptomatology indicated a transverse cord lesion. This was certainly not true of the present series in which the majority of patients ultimately presented complete paraplegia and sensory loss. Even with these findings, the spinal cord not infrequently showed unexpectedly mild changes. This fact emphasizes the possibility of functional recovery if the tumor is removed. On the other hand, it also emphasizes that functional disability need not be reflected by severe morphologic alteration.

The experiments of Tarlov[25,50,51] in which the cord was quickly compressed by the rapid inflation of an extradural balloon, produced cord cavitation in those animals which survived for longer periods. Such cavitation is rare in human beings, even when the onset of paraplegia is instantaneous and survival is long. The rarefaction and vacuolation Tarlov described as the result of gradual compression of the dog spinal cord more accurately parallels the pathologic picture seen in man.

Woodard and Freeman[57] ligated and sectioned several pairs of thoracic nerves with

their radicular vessels in order to produce cord ischemia. These experiments, performed on dogs, resulted primarily in loss of dorsal neurons and cavitation of the midline gray matter posterior to the central canal. Again, this is not similar to the human disease, although, in the latter, the radicular vessels are often surrounded by the neoplasm.

The pathogenesis of the spinal cord lesions due to contiguous metastasis remains obscure. Simple direct pressure is not the whole answer – nor do the usual lesions appear to be the result of arterial occlusion. Interference with venous return, as suggested by Wilson and Rupp[3] and by Greenfield,[58] may well be an important factor. The common histologic picture is consistent with such alteration, and the frequent clinical improvement following simple laminectomy and decompression also supports this possibility.

SUMMARY AND CONCLUSIONS

Clinical and pathologic data are presented concerning 127 autopsied patients with involvement of the spinal cord and cauda equina by metastatic neoplasms. Carcinomas of the lung, breast, and kidney and malignant lymphomas were the most common primary tumors.

The clinical features which distinguish metastatic tumors from primary extramedullary neoplasms are described, and the rapidly progressive nature of the symptoms in the former is stressed. Important differences exist in the clinical and radiologic behavior of metastases from different primary sources.

The following features are invariable in involvement of the spinal cord by metastasis from carcinoma of the breast: [1] a known primary site; [2] a history of pain in the back or pain in a radicular distribution; [3] radiologic evidence of multiple vertebral lesions; and [4] a relatively gradual progression.

Carcinoma of the lung, in contrast, may present as disease of the spinal cord, be unassociated with pain, show no vertebral lesions to radiographic examination, and produce instantaneous or extremely rapid onset (less than forty-eight hours) of paraplegia. The clinical behavior of metastasis from carcinoma of the rectum and multiple myeloma resembles carcinoma of the breast, while malignant lymphomas and carcinoma of the kidney more closely resemble carcinoma of the lung. Survival is shortest in carcinoma of the lung and in cases of rapid progression to paraplegia.

Dissociation between motor and sensory dysfunction and the importance of the false sensory level, which may occur below the site of the lesion, are discussed. Sacral sparing with extradural neoplasms is recorded.

The syndromes accompanying metastasis at different levels of the cord are examined. Thoracic lesions are most likely to be associated with fulminant onset and progression.

Herpes zoster may occur prior to, coincident with, or after the development of symptoms of cord disease and is an accurate index to the site of the lesion.

Lumbar puncture may reveal no manometric block in paraplegic patients. The highest spinal fluid proteins occur in lesions of the cauda equina. In this series, lumbar puncture was not attended by complications.

The limitations of lumbar myelography in the management of these patients are stressed, and we recommend that cisternal and lumbar myelography be combined.

Of 38 patients who had operation, 6 had striking improvement. Operation is unlikely to be valuable when (1) the patient manifests a flaccid, areflexic paraplegia or paraplegia has developed in less than seventy-two hours, (2) sensory loss is complete, and (3) the primary tumor is a carcinoma of the lung. Spastic paraplegia with flexor spasms of twenty-six days' duration has been relieved by operation.

The pathologic changes in the spinal cord are quite variable and consistent clinicopathologic correlation is not possible. The gray matter is spared to a large extent, while the white matter is most often affected by an edematous type of malacia distinct from infarction. Intramedullary metastasis was found in 2 of the 127 patients. Dorsal column, ascending demyelination is rapid, but the other sensory tracts are irregularly involved.

The authors gratefully acknowledge the assistance and support of Dr. H. M. Zimmerman.

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Hidden neurologic mechanisms in motor function restitution

Experiments with cortical lesions in monkeys

A. M. Lassek, Ph.D., M.D., and Sara L. Emery

RESTITUTION OF motor function is one of the most important phenomena occurring in lesions of the central nervous system. It is generally believed that some degree of recovery follows every injury to this part of the body. In some instances, it may be remarkable, even among primates. For example, Ades and Raab[1] and Denny-Brown[2] reported recovery within a month after unilateral lesions of the motor cortex in the monkey. In spite of its great significance in medicine, there is no agreement as to the neurologic mechanisms responsible for the improvement. This can be demonstrated by the number of theoretic explanations proposed regarding restitution of motor function. Lashley[3] notes them as follows:

1] Lesions which produce motor deficits do so by diaschisis or depression. After a period, the affected center or centers recover and symptoms disappear.

2] Remaining nerve tissue reorganizes spontaneously, independent of regeneration or reeducation.

3] Retraining is important.

4] There is a large safety factor existing within the nervous system whereby many potential conditioned reflex paths can be brought into use.

5] Every part of the nervous system participates in every function so that recovery must involve a complete reorganization of the unaffected parts.

6] Compensatory hypertrophy occurs in the remaining corticospinal pathway after cerebral lesions, especially in cases of infantile hemiplegia.

Some authorities believe that the plasticity of the nervous system is so great that it permits almost unlimited possibilities in respect to motor function restitution.

During the past half century, the afferent system has been considered an important possible inciting and controlling force in motor function.[2,4–12] Most of this has been on a theoretic basis because of the complexities involved in the mechanism of movement. The sensory pathways are numerous and scattered throughout the central nervous system and evade most neurologic, investigative approaches. One experimental method which may give clues on this subject is the electrophysiologic; another utilizes certain drugs, especially those in the hypnotic series. The latter can be employed in animals subjected to placement of definite circumscribed lesions involving the somatic motor apparatus followed by various degrees of restitution of function.

The purpose of the present investigation is to study the effect of a relatively powerful barbiturate, sodium phenobarbital, in monkeys according to the above standards. It is believed that such a project will provide information showing that the remaining neurologic mechanisms responsible for return of motor function are markedly affected by the injections of this drug.

MATERIAL AND METHODS

Bilateral lesions of area 4 were made at one operation in 9 Macaca mulatta monkeys having an average weight of 5.3 lb. The exact delimitation of the motor cortex was not held

From the Department of Anatomy, Boston University School of Medicine.
This investigation was supported by a grant from the United Cerebral Palsy Research and Educational Foundation, Inc.

to be highly important since the intent was to produce a temporary state of incomplete prostrating bilateral paralysis, offering the possibility for some return of motor function. In the majority of instances, the motor area was outlined by means of electrical stimulation. The tissue was removed by means of the suction technic in each animal.

Sodium phenobarbital, 50 mg. per cubic centimeter of water, was given intraperitoneally in 51 injections to 8 animals; total dosage ranged from 100 to 400 mg., with an average of 212 mg. In general, it was found that 86 mg. per kilogram of body weight was sufficient to produce the desired hypnotic effect, the range being 74 to 100 mg. per kilogram. The interval between the operation and initial administration varied from one to forty-seven days, averaging 18.6 days. When the drug was first given, recovery had occurred in all animals to the extent that they could sit; the majority were also able to walk, run, and climb in a primitive fashion. The mean spacing of injections was eleven days, with a range from one to forty-two days. Normal macaques were drugged with equivalent doses of the preparation to serve as controls in each series. The experimental monkeys were allowed to survive for an average of 169 days, the variations being between eight days and two and one-half years (still living). The effect of the drug was compared with that of Sodium Amytal.

In addition, an attempt was made in one animal to keep it in a state of motor prostration as long as possible by giving daily graded doses of sodium phenobarbital.

Each monkey was examined neurologically at frequent intervals after awakening until the effects of the drug could no longer be detected. The time factors given for motor prostration do not include observations that were made during the night, so, in some cases, they are minimal.

With the exception of the animal kept alive for additional injection experiments, the animals were sacrificed and histologic studies of the extent of the lesions made using cresyl-violet stain. The fine anatomy of the pyramidal tract fibers in the brain stem and spinal cord was also examined in each instance; sections were stained with silver nitrate, protargol, or Weil's myelin sheath methods.

RESULTS

It was found that a hypnotic dosage of sodium phenobarbital, given to an experimental monkey showing restitution of motor function, caused the animal to awaken in a state of motor prostration lasting for as long as 2 to 10 times the sleeping interval. In 51 injections, the duration of this advanced degree of paralysis amounts to a total of 846 hours; the average is nineteen hours, and the range is from twenty minutes to seventy-two hours. The stronger the dosage, the longer the symptoms.

While in this motor state, the animals initially lie on their sides, helpless and unable to move even when prodded. At most, they make only weak pawing movements with their upper extremities. Symptomatology may be exaggerated over that seen immediately after the operation. Eventually, they become able, with effort, to grasp the sides of their cages and elevate themselves to a sitting position. When tested on the floor, however, without something suitable to grasp above, an animal might remain immobilized for as long as twenty-four hours more. During the entire period of motor prostration, the monkeys are otherwise alert and sensitive. The defects produced with sodium phenobarbital are more prolonged than with Sodium Amytal.

Other obvious deficits noticed after recovery from postinjective motor prostration are disturbed postural equilibrium, incoordination in walking and running, weakness, slowness, easy fatigue, and inability to use hands. These characteristics may last for two to three days after spaced injections.

One monkey was kept in an almost complete state of conscious motor prostration for a period of a month by daily injections of sodium phenobarbital; however, the animal developed pressure sores, and the experiment was discontinued.

Death resulted in one monkey after a 400-mg. (160 mg. per kilogram) dose of sodium phenobarbital. Unconsciousness lasted for forty-six hours, and the animal remained in a state of conscious motor prostration for the remaining 5 days of life.

Normal control monkeys injected with sodium phenobarbital exhibited incoordination and disturbed balance for several hours; no posthypnotic paralysis occurred.

In general, the extent of the superficial lesions in the precentral gyrus conformed to that of area 4, with minor variation to produce the degree of incomplete paralysis desired.

The picture of the fibers in the pyramidal tract of the medulla is typical of what has been noted previously for area 4 lesions by a number of investigators. Many axons, mostly of small caliber, remain intact; some medium and most large-sized ones disappear.

DISCUSSION

The results of the experiments suggest that the neurologic mechanisms involved in producing cortical paralysis remain basically unaltered and hidden during the phenomenon of motor restitution; whatever recovery occurs masks the underlying defect so that the phenomenon probably repairs around it. This is shown by the fact that repeated injections of sodium phenobarbital in a partially paralyzed but mobilized monkey over a thirty-month period always results in motor prostration. This residual defect remains chronic, exhibiting at most a minor change.

What part or parts of the central nervous system sodium phenobarbital acts upon is the main question in our investigation. Apparently, this cannot be answered unequivocally. Goodman and Gilman[13] found evidence indicating that barbiturates affect all segmental levels, with the cerebral cortex and reticular activating system being most sensitive; the cerebellar, vestibular, and spinal systems less sensitive; and the vital medullary systems least sensitive.

These workers further believe that [1] elevation of the threshold of neurons by stabilization of the cell membrane and [2] prolongation of the time for recovery from excitation are the two outstanding properties of the barbiturates, established beyond a doubt by electrophysiologic and electroencephalographic investigations.

If it is assumed that the drug used has a primary predilection for such centers as the cerebral cortex and reticular activating systems, known to have to-and-fro connections, it could not have acted upon the motor cortex in our series because this center was ablated. The absence of the neurons involved in the removal of area 4 is important, as it was shown that motor prostration does not occur in normal animals. It may be that sodium phenobarbital affects the brain-wave patterns to cause derangement of function. Any attempt to pursue the subject further would be speculative and theoretic because of lack of pertinent information.

The 2,500 known barbiturates constitute a group of chemicals of which some have been widely studied in respect to their locus of action upon the central nervous system. We hope to try the other barbiturates as well as numerous nonbarbiturates. The results may offer further information on the important question of neurologic mechanisms in paralysis and restitution of motor function.

Watson and Kennard[14] injected sodium phenobarbital subcutaneously in nonhypnotic doses into monkeys from which areas 4 and 6 were extirpated unilaterally. It was concluded that a marked slowing in rate of recovery occurred with eventual retardation in motor function. Our results harmonize with this finding basically, but we have followed a different approach, aiming to produce a typical and characteristic paralysis after hypnosis with this drug.

A practical feature of observations of this nature is in respect to tests which may be developed for detecting latent motor deficits in man. Teng and Bender[15] have made a start in this direction. They used Sodium Amytal intravenously, 0.5 gm. per 10 cc. of distilled water, at a rate of 0.05 gm. per minute in selected human patients with a background of unilateral motor difficulty. They concluded that it is a simple and sensitive procedure for detecting motor weakness of central origin. By contrast, we have used monkeys with bilateral cortical lesions, a stronger drug injected intraperitoneally, and a higher dosage.

The effect of Sodium Amytal has been compared with sodium phenobarbital in our series, and we find that the latter produced a much greater motor inadequacy in our partially paralyzed monkeys.

The results obtained have been such that we believe sodium phenobarbital may be of some value in detecting hidden neurologic mechanisms, or lack of them, in appropriate cases in man.

CONCLUSIONS

1. Intraperitoneal injections of sodium phenobarbital in certain nonlethal dosages produce a state of motor prostration in monkeys showing restitution of motor function after superficial, bilateral lesions of area 4.

2. The duration of this deficit is from 2 to 10 times longer than the period of hypnosis produced.

3. This general result has been obtained repeatedly after spaced injections, extending over an interval of thirty months in one animal.

4. In one case, a monkey has been kept in a continuous state of motor paralysis for as long as a month by giving daily graded doses of the barbiturate.

5. It is suggested that the underlying neurologic mechanisms remaining after the lesions are made are unaffected throughout and are masked by the phenomenon of restitution of motor function.

6. Sodium phenobarbital is a relatively powerful barbiturate which, when injected intraperitoneally into the monkey, reveals latent motor deficits more easily than Sodium Amytal. It is believed that sodium phenobarbital may also prove more efficient in this respect than the latter in man.

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The diagnostic problem

Epilepsy of late onset

R. B. Raynor, M.D., R. S. Paine, M.D.,
and E. A. Carmichael, F.R.C.P.

SEIZURES THAT COMMENCE after childhood have posed a diagnostic problem for many years. In patients whose seizures do not start until after they are 20 years old, the most pertinent question is whether or not they are harboring a neoplasm. Upon the probable answer to this question must depend the vigor with which the diagnostic workup is to be pursued. Such tests as air encephalography, ventriculography, and arteriography are not without morbidity and even mortality.

Most writers attribute the majority of seizures between the ages of 35 to 55 to neoplasm. Penfield and Erickson[9] list trauma and neoplasm as the most common causes of seizures which start in patients 20 to 55 years old, and, in his later volume with Jasper,[10] Penfield gives the same statistics as in the earlier work.

The onset of seizures after childhood is not rare. Gowers[8] stated that 89.5% of all epileptics had their first seizure before age 29. Oatman,[7] however, studying male veterans, found that only 21% had onset of the disease before age 20. Various authors cite intermediate values, although most quote a value under 25% in their statistics for epilepsy of late onset. Epilepsy of late onset (as defined here, seizures starting after the patient reaches the age of 20) is, therefore, relatively common.

MATERIAL

All cases of epilepsy of late onset first seen by one of us (E.A.C.) between 1945 and 1954 comprise the present study which originally included 151 patients. All patients with a history of febrile convulsions in infancy or childhood were excluded, as were all patients who were thought to have posttraumatic epilepsy. Of the 151 patients, 10 could not be reached for follow-up information. Of the remaining 141, 16 had cerebral tumors; 125 apparently did not.

The initial symptom in all was epilepsy, which began after the age of 20. Some patients had been seen previously by other doctors but were then referred to one of us (E.A.C.) either for further evaluation or because neurologic signs had appeared after previously normal examination.

RESULTS

Of the 141 patients successfully observed, 16 had supratentorial intracranial tumors. Histologically, the tumors included 5 astrocytomas, 4 meningiomas, 3 oligodendrogliomas, 3 angiomas, and 1 cholesteatoma. In 13 patients, the diagnosis was made on initial admission to the National Hospital for Nervous Diseases, but in 3, after intervals of nine months, twelve months, and three years. The delay in diagnosing the first 2 of these patients was probably, in retrospect, based on a normal or borderline air encephalogram at the initial admission. In 1 patient, a small temporal oligodendroglioma was found at temporal lobectomy done nine months later for intractable fits; in the other, progression of symptoms led to a repeated and abnormal air encephalogram a year later. In the third patient in whom diagnosis was delayed, a right temporal lesion was suggested by the initial air encephalogram,

From the Neurological Research Unit, Medical Research Council, The National Hospital, Queen Square, London, W.C.1.

Dr. Raynor's present address is the Department of Neurological Surgery, Neurological Institute, Columbia-Presbyterian Medical Center, New York City.

Dr. Paine's work was carried out during tenure of a special clinical traineeship, National Institute of Neurological Diseases and Blindness, National Institutes of Health, U.S. Public Health Service.

TABLE 1

DATA ON 141 PATIENTS WITH EPILEPSY OF LATE ONSET

	Patients with tumor	*Patients without demonstrated tumor*
Total number of patients	16	125
Sex		
Male	8	62
Female	8	65
Age at onset of seizures		
20 to 30	4	46
30 to 40	6	37
40 to 50	2	32
50 to 60	3	9
60 to 70	1	1
Significant history		
Severe headaches	4	5
Abnormal birth	–	1
Meningitis	–	2
Head trauma*	5	17
Seizure type		
Grand mal (nonfocal)	5†	96
Focal motor	8	15
Temporal lobe	3	14
Miscellaneous	1	3
Neurologic examination		
Normal	2	111
Abnormal	14	14
(Papilledema)	(4)	(0)
Otologic examination		
Normal	2	29
Abnormal	2	8
Electroencephalogram		
Normal	2	46
Diffusely abnormal	4	58
Focally abnormal	8	21
Not tested	2	0
Roentgenograms		
Plain films		
Normal	12	122
Abnormal	4	3
Air study		
Normal	3	53
Abnormal	10	4
Arteriogram		
Normal	0	18
Abnormal	8	1
No contrast study done	0	66
Years from first seizure to diagnosis of tumor		
Under 1	4	–
1 to 5	4	–
5 to 10	5	–
10 to 15	4	–
Follow-up (years)		
3 to 5	–	12
5 to 10	–	30
10 to 15	–	44
Over 15	–	39

*Head trauma not thought to be significant in the etiology of the seizure

†One of these patients later (four years after onset) began to have focal motor seizures.

but a biopsy taken at operation showed no tumor tissue. Continued intractable fits led to a temporal lobectomy three years later, when a small oligodendroglioma was found.

If seizures are attributed to cerebral neoplasm in patients with tumors, the length of time between the onset of fits and the definitive diagnosis is somewhat surprising. Fits had occurred in 4 patients for less than one year; in 4 for one to five years; in 5 for five to ten years; and in 4 for ten to fifteen years.

These data suggest that a normal air encephalogram or arteriogram, plus a follow-up period of not less than three years without adverse developments, is probably sufficient to rule out a tumor and that a follow-up period of fifteen years is probably similarly indicative without a contrast roentgen study.

Of the 125 patients who apparently do not have tumors, 56 satisfy the first criterion, 20 the second. Further, the statistics will probably not be altered significantly by the discovery of tumors in the remaining 49 patients not included above—as all of the cases with tumors were diagnosed by contrast roentgenograms not more than three years from their first National Hospital visits.

Actually, as will be discussed below, only 2 patients with tumors failed to present abnormal physical signs when first seen as outpatients. Some of them had been having fits for ten or more years but did not know when the abnormal signs first developed. The 2 who had negative neurologic examinations when first seen had each had focal seizures (and 1 a focal electroencephalogram as well). Angioma was found after one year in one patient and initially in the other.

It thus seems reasonable to compare the 16 patients having tumors with all of the 125 not so far giving evidence of tumor. The length of negative follow-up for the later group has been over fifteen years in 39 patients, ten to fifteen years in 44, five to ten years in 30, and three to five years in 12 patients. Results of this comparison are summarized in Table 1.

AGE OF ONSET

The case material is divided chronologically into 5 groups. Each comprises a ten-year period between the ages of 20 and 70. No extreme difference was found in the number of patients who had seizures for the first time in the ten-year periods from ages 20 to 50. In the subsequent groups, the number of patients decreased appreciably. The distribution of patients at age of onset of seizures was as follows:

Age of onset	*16 patients with tumor*	*125 patients without tumor*
20 to 30	4	46
30 to 40	6	37
40 to 50	2	32
50 to 60	3	9
60 to 70	1	1

It will be noted that tumors were found in 4 out of 14 patients having first seizures after the age of 50.

PHYSICAL FINDINGS

At the time they were seen at the National Hospital, 28 patients had abnormal findings on neurologic examination. Of these patients, 14 had tumors, but, in the remaining 14, no evidence of tumor was found.

Of the 14 patients without tumor, 5 had only minimal findings: 3 had nystagmus, and 2 had anisocoria. The other 9 patients had abnormalities which are usually considered more significant; 2 had homonymous quadrantic visual field defects; 2 had slight left hemipareses, but air encephalography was normal in both and arteriography normal in 1. Both have been observed for six years and have developed no new symptoms. In 2 patients, pes cavus and extensor plantar responses were found; 1 of the patients had normal air-encephalography and arteriography, and both patients remain unchanged after three years. One patient had an absent left corneal reflex and 1 had left Horner's syndrome with a fifth cranial nerve palsy and hypesthesia. No explanation is available for these findings, but air encephalography was negative in each.

TYPE OF SEIZURE

Focal seizures occurred in 23 patients; 8 of the 16 patients with tumors and 15 of the 125 patients without tumors were in this group; 3 patients who had tumors developed postictal paralysis.

Nonfocal grand mal seizures were found in 5 patients with tumor and 96 patients without tumor. Possibly, some of these patients had, in fact, focal onset, but a description by a competent observer was not always available.

Temporal lobe seizures occurred in 17 patients; 3 were in the tumor group. Temporal lobe seizure here is taken to mean a temporal lobe focus in the electroencephalogram, together with clinical manifestations of the psychomotor variety. No patients in this study happened to satisfy only one of these criteria.

Seizures were classified as miscellaneous in 4 patients. This group included 1 patient with tumor. Several patients had more than one type of seizure.

ELECTROENCEPHALOGRAM

All patients without tumor had an electroencephalogram, as did 14 of the patients with tumor. In the former group were 46 normal, 58 nonfocally abnormal, and 21 focally abnormal records. The tumor group consisted of 2 normal, 4 abnormal but nonfocal, and 8 abnormal focal electroencephalograms.

ROENTGEN EXAMINATIONS

All patients had plain films of the skull made; 7 were reported as abnormal. Of patients with these abnormalities, 3 were in the group without tumor. Displacement of the pineal gland was found in 2, both of whom had normal air studies. Surgery was performed on a patient with superficial cerebral calcification, but no tumor was found.

Further diagnostic studies were performed on all of the patients with tumors. An air study was done in 13 patients; 10 were abnormal. Arteriograms were made in 8, and all were abnormal.

Of the 125 patients presumed not to have tumor, 66 had no further roentgenograms. Of these 125 patients, 59 did have contrast tests. There were 53 normal and 4 abnormal air studies, and 18 normal and 1 abnormal arteriograms; 1 patient had a slight septal shift to the right on both air and dye studies, but no lesion was found at exploration; 1 patient had an elevated left temporal horn on the air encephalogram but had a normal arteriogram. The air study on the third patient suggested a left juxtathalamic lesion, but the patient has remained well for sixteen years since the test. The fourth abnormality was a slight dilation of one lateral ventricle on the air study.

OTOLOGIC STUDIES

Otologic studies were done on 41 patients according to the method of Fitzgerald and Hallpike.[2] Abnormalities were found in 10 patients and consisted of directional preponderance in all. In 4 patients with tumor, 2 had abnormal responses; in 29 patients without tumor, 8 abnormal results were found.

PAST HISTORY

Among 4 patients who had tumors, severe headaches had occurred for many years. In the group without tumors, 5 patients had a prolonged history of headaches; 2 patients without tumors had had meningitis, and 1, birth trauma.

DISCUSSION

Patients who first experience seizures after the age of 20 usually do not have tumor. If several diagnostic criteria are fulfilled, a reasonably accurate prognosis can be made, and the patient can be reassured. In the 141 patients, only 16, or 13.6%, have so far been found to have cerebral tumors. Walker,[11] after studying 100 patients with convulsive seizures starting in adult life, reported a comparable incidence of 16% for tumors. Livingstone[4] found only 3 tumors in 689 cases of epilepsy of late onset, but his patients all had been neurologically or neurosurgically evaluated before referral to the Epilepsy Clinic.

Only 2 patients in the present series who were normal at the initial physical examination were found later to have cerebral tumors. Of the 125 patients in this series who are believed not to have tumors, 14 had some abnormalities on physical examination, but these were severe in only 4 patients. The meaning of the normal examination becomes more apparent when these figures are restated. In 113 patients with a normal neurologic examination, only 2 are known to have tumors. In another series of 313 patients with brain tumor, 12% initially complained only of seizures, and only 7.4% failed to show other abnormalities within a very short time.[8] Within one year, only 4.1% of these patients had no additional symptoms.

When the type of seizure is analyzed, the axiom that focal fits are indicative of tumor is found to be only a partial guide. Half of the patients with tumor had focal seizures, but 12% of the patients without tumor had fits of this type. In other series of patients with seizures who did not have tumors, about 11% of the seizures were of the focal variety.[4,6]

Of interest is the occurrence of posticta paralysis in 3 of the 8 patients with tumor and focal seizures – there were no such findings in the group without tumors.

From the small amount of material available, temporal lobe seizures do not appear to be of diagnostic significance with regard to tumor. White and others[12] have found that, in patients over 50 years old, most focal seizures are of the temporal lobe variety. However, his definition of focal seizures may include electroencephalographic diagnoses without focal physical features of the fit itself.

The electroencephalogram correlates closely with the clinical type of seizure. About half of the tumor cases had a focus, as did 16.8% of the nontumor group.

A history of trauma does not appear to be of any help in differentiating the cause of the fits. A suggestive history of head injury was obtained in the cases that had tumor more often than in the group that did not have tumor. In both groups, the trauma was not thought to be a significant factor in the causation of the seizures. (Cases that were frankly posttraumatic were eliminated from consideration.)

Various roentgenograms were done in all patients. The plain skull films were found to be the least informative – as would be expected. Even in patients with tumor, roentgenograms were abnormal in only 4 of 16 patients. No contrast studies were made in 66 patients without evidence of tumor, but 20 have been followed fifteen years or longer without evidence of cerebral neoplasm.

All of the patients with tumors had contrast roentgenograms. Lumbar air encephalograms or direct ventriculograms were abnormal and indicated the presence of a mass lesion in 10 of 13 patients in whom they were carried out. In 1 other patient, the ventricular filling was not fully satisfactory; an arteriogram was made which revealed a posterior temporal angioma. In 2 other patients, as already discussed, initial air encephalograms were normal but tumors were found nine and twelve months later on further investigation after symptoms had progressed. Arteriography gave abnormal results in all of the 8 tumor patients subjected to it.

In the nontumor group, 4 patients had abnormal air studies and 3 of these were thought possibly to be significant, but further evaluation (arteriography in 1, operation in 1, and sixteen-year follow-up in 1) failed to confirm the initial impression. In a group of 64 patients with seizures in the military service, Marshall and Whitty[5] found 5 abnormal pneumoencephalograms. Of their patients, 10 had abnormal neurologic examinations. However, in only 16 patients was the history of seizures of three or more years' duration, and some of their cases were due to closed head injuries. Two patients with tumors were included in their group. Martin and McDowell[6] found abnormal air studies in 3 out of 65 patients over 34 years old who had normal neurologic examinations and seizures. Berlin,[1] using a group over 35 years old, found 4 abnormal pneumoencephalograms in 57 patients without tumors who developed seizures.

In all patients of the present study, a minimum of three years of follow-up was available. Although no gross alteration in the present statistics should occur, more tumors may yet be found in the group that is now classified as not having tumors. Parker,[8] in his series of 313 cases of brain tumor with convulsions, found 38 with seizures as the initial symptom, but only 13 had not developed other manifestations within a year. He had 1 patient who was followed twenty-three years, another seventeen years, and another fifteen years before further symptoms appeared. This is a higher percentage of delay than in the present group, but Parker was concerned with brain tumors primarily, while this series is concerned with epileptics. The difference in orientation may well weight the material.

CONCLUSIONS

Epilepsy beginning after the age of 20 is statistically less likely to be due to cerebral tumor than some have stated, although tumors admittedly occur among such patients more

frequently than in younger age groups. Tumors have been confirmed in only 16 out of 141 cases of epilepsy of adult onset, an incidence of 11.3%. It is conceded that additional tumors may yet be found in the nontumor group, but the statistics and the conclusions drawn from them will probably not be greatly altered.

The statistical probability of tumor is considerably increased with any of the following circumstances:

1] The presence of abnormal physical neurologic signs. This is the best single criterion, and 50% of the patients in this study who presented abnormal neurologic findings had tumors. Further, 14 of the 16 patients with tumors had abnormal neurologic signs when first seen.

2] The occurrence of seizures of focal motor character or with focal sensory aura. This is accompanied by a 35% incidence of cerebral tumor. Of 16 patients with tumors, however, 5 had nonfocal fits as far as is known. However, temporal lobe attacks—not included with focal motor seizures—carried only 18% likelihood of tumor in the present study.

3] The presence of focal abnormality in the electroencephalogram. This was accompanied by a 28% incidence of tumor. However, only 8 patients with focal electroencephalographic abnormality were found among 14 tumor patients who had electroencephalograms; 6 of the 8 were also known to have been having focal motor fits.

4] Initial onset of epilepsy after the age of 50 years. Tumors were found in 4 of 14 patients.

Arteriography or air encephalograms can be expected to define a tumor, although in 2 patients, the air encephalogram failed initially. While each patient who has epilepsy of late onset must be evaluated individually—including the reliability of future observation to be expected—probability of brain tumor apparently is not sufficient to justify contrast roentgenogram investigation in every such patient. In general, a proper indication for such investigation would be any of the 4 criteria listed above. At least 1 of these criteria was satisfied in all the 16 tumor patients identified in this study, and only 1 patient failed to satisfy at least 2 of them.

It must be borne in mind that tumors of the brain may produce epilepsy for long periods of time without killing the patient and without becoming obvious. Of 16 patients with tumors, 9 had been having fits for more than five years and 4 for more than ten years. All of these examples of long-delayed diagnosis, however, presented abnormalities on initial neurologic examination, although it is not known how long the abnormalities may have been present. Continued contact, regular reexamination, and reconsideration are necessary in any epileptic patient with late onset not initially investigated by contrast roentgenograms. Even if the roentgenograms are initially negative, a tumor may yet appear after at least as long as a year—and very probably longer.

SUMMARY

1] A follow-up study is presented of 141 patients with epilepsy of onset after the age of 20 who were seen at the National Hospital for Nervous Diseases, London.

2] Only 16 have been shown to have cerebral tumors. Of the others, 56 are believed not to have tumors on the basis of anatomic investigations by air encephalography or arteriography or both, plus a follow-up period of not less than three years; 20 other patients are believed not to have tumor on the basis of a fifteen-year follow-up alone. Additional tumors may yet be found among the remaining 49, but reasons are presented why these should not be numerous nor invalidate statistical comparison of the 2 groups.

3] The following circumstances significantly increase the likelihood of tumor to 28 to 50% and warrant contrast roentgenogram study:

- Abnormal physical neurologic signs, the best single criterion
- Focal motor seizures or seizures with focal sensory aura
- Focal abnormality in the electroencephalogram (rare in this study unless the seizures were also focal).
- Initial onset of fits in a patient over 50 years old.

4] Anatomic investigation is ordinarily not warranted in epileptic patients of adult onset who do not satisfy at least one of the above criteria—provided a satisfactory future follow-up can be made.

5] Even epilepsy of more than ten years' duration may be based on cerebral tumor—

without the tumor killing the patient or being obvious. Failure to find abnormal physical neurologic signs in a patient who has been having fits for as long as three years, however, is a strong argument against the presence of a tumor, unless the seizures or the electroencephalograms are focal or the patient is more than 50 years old.

6] Even a normal air encephalogram at initial investigation does not rule out the possibility of tumor, and this diagnosis was made subsequently in 2 patients who were reinvestigated after a year's time because signs and symptoms had progressed. The need for follow-up is thus not obviated by any initial study.

ACKNOWLEDGMENT

We are indebted to our colleagues in the Applied Electrophysiology, Otological, and Radiological Departments for the examinations carried out by them.

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Hypoglossal-facial anastomosis for treatment of facial paralysis

L. A. Kessler, M.D.,* J. Moldaver, M.D., and J. L. Pool, M.D.

THE TREATMENT of peripheral facial paralysis by hypoglossal-facial nerve anastomosis or crossing was first described by Körte in 1901.[1] Practical experience and theoretical grounds[2] have led us to prefer XII–VII rather than XI–VII[3,4] cranial nerve crossing.

Clinical and electrical studies have been made of 14 patients. The surgical technic is so well known that no further description is necessary.[2,4] Most of these operations were done by one of us (J.L.P.).

CASE MATERIAL

Of the 14 patients with hypoglossal-facial nerve crossing one to twenty-one months after onset of facial paralysis, 9 had surgery in less than two months, and 5 at four, eight, nine, fifteen, and twenty-one month intervals (Table 1). The shortest follow-up period is four months, the longest four years. In 13 patients, facial palsy followed an operation for removal of an acoustic neurinoma; in 1 patient, palsy followed surgical ablation of the labyrinth for Ménière's disease.

In 10 patients, the twelfth nerve was completely divided close to the tongue and mobilized and sutured to the distal portion of the seventh cranial nerve. In 5 of the 10 patients the descendens hypoglossi was then mobilized and sutured to the distal end of the twelfth nerve, while in 4, the hypoglossal nerve was split longitudinally so that approximately two-thirds of its diameter was used for suture to the facial nerve; the remainder was left intact. These 2 measures, designed to preserve or to provide innervation of the tongue, are referred to in Table 2 and in certain figures as hypoglossal nerve reinnervation or reconstruction.

Follow-up studies: 10 patients have had repeated nerve and muscle stimulation studies and chronaxy measurements; 6 have had, in addition, electromyographic recordings made from the face, as well as from the tongue musculature. In the nerve and muscle stimulation tests, square wave currents were used. Coaxial needle electrodes were used for electromyography.

RESULTS

Our results at operation have been classified as successful or poor. By successful we mean [1] practically normal facial tone returns with symmetric nasolabial folds and eye fissures (Figs. 1A, 1B, 2E, 2F); [2] the eye can be closed (Figs. 1B, 2A, 2B); [3] the corner of the mouth can be raised (Figs. 1C, 1D, 2C, 2D); and [4] no gross impairment in speech. Poor results are those not complying with the above criteria, although adequate follow-up time has elapsed.

On this basis, results in 11 of the 14† patients are classified as successful and 3 as poor. Of patients classified as poor results, however, 2 show some evidence of nerve regeneration. For instance, 1 patient (J.W.) can contract the orbicularis oculi muscle and elevate the corner of his mouth to a slight degree, while stimulation of the facial nerve results in a fair response in the frontalis, orbicularis oculi superior, zygomaticus, risorius, and chin muscles. All muscles supplied by the facial nerve, moreover, showed only moderately elevated chronaxy figures as seen in reinnervation.

The second patient (M.M.) has a little voluntary motion at the corner of her mouth. Electrical tests showed that stimulation of the affected facial nerve resulted in a partial response in the quadratus labii superior and in

From the services of Neurological Surgery and Neurology, The Neurological Institute, Columbia-Presbyterian Hospital, New York

*Traineeship, BT 180(C2), from the National Institute of Neurological Diseases and Blindness, Public Health Service

†Now 14 of 17 patients

TABLE 1
CASE SUMMARY

Case		Sex	Age	Primary Operation	Interval Between Paralysis and Nerve Crossing	Follow-up Period (Months)	Result
1	A.R.	M	20	(A), L.	3 weeks	48	Successful
2	M.D.	F	47	(A), L.	1 month	48	Successful
3	B.A.	F	35	(A), R.	1 month	48	Successful
4	B.J.	F	34	(A), R.	1 month	44	Successful
5	J.B.	M	49	Surgical trauma mid. ear, R.	8½ months	42	Poor
6	E.G.	F	45	(A), R.	1½ months	36	Successful
7	H.M.	M	53	(A), R.	1 month	36	Successful
8	M.M.	F	55	(A), R.	21 months	29	Poor
9	J.W.	M	25	(A), R.	3 weeks	11	Poor
10	V.L.	F	42	(A), R.	15½ months	11	Successful
11	H.P.	F	55	(A), L.	1½ months	8	Successful
12	L.S.	M	40	(A), R.	3 weeks	7	Successful
13	B.Q.	F	37	(A), L.	9½ months	5	Successful
14	F.S.	M	38	(A), R.	4 months	4	Successful

(A) — Acoustic tumor.

the orbicularis oris inferior muscles, but not elsewhere. Direct testing of the facial muscles showed high chronaxy figures and slow responses, as seen in denervation, while the amplitude of contractions was small and characteristic of a significant loss of muscular structure. The third patient (J.B.) was contacted only by mail, and, despite photographs, critical evaluation was impossible.

Results of electrical studies in the successful cases were essentially alike. Good responses were obtained on stimulation of the facial nerve in most of the muscles it supplies. Good amplitude of the contractions of the muscles either on direct or indirect stimulation was found, and a progressive drop of the chronaxy figures occurred which was consistent with satisfactory neurotization. As seen in muscles with good nerve supply, contraction of muscles to direct stimulation became more rapid. Electromyography showed good firing of motor units with volition (Figs. 3, 4, 6) and relatively little evidence of fibrillations (Fig. 4) or monophasic positive waves of denervation.

RESULTS OF TONGUE FUNCTION (Table 2)

All the patients had some atrophy of the tongue, but in none was speech or swallowing significantly impaired. None of these patients was a public speaker or singer.

Motion of the tongue was possible in all directions in all patients, with remarkably little deviation on protrusion (Fig. 1E and F). Of 5 patients with anastomosis of the descendens hypoglossi, 2 (V.D., M.M.) showed only minimal lingual atrophy, good motion in all directions, and excellent electrical responses (Fig. 8). While a third patient (B.Q.) has had no return of function thus far, it is probably too early to be expected (Table 1), even though electrical studies showed some evidence of neurotization on stimulation of the nerve and in electromyographic recordings. Information is not available on another patient (J.B.), while the fifth patient (H.M.) has no evidence of functional or electrical reinnervation of the affected side of the tongue.

In 3 of 4 patients (J.W., M.D., and A.R.) whose twelfth nerves were split, electrical tests show negligible tongue atrophy and ex-

Figure 1

(A and *B)* H.P. and B.S. Excellent facial symmetry and tone at rest. *(C* and *D)* L.S. and V.L. Pleasant smile seven and eleven months respectively after nerve repair. *(E)* L.S., same patient as in *C*. Minimal tongue atrophy seven months postoperatively with no twelfth nerve reconstruction. *(F)* M.D. Minimal left tongue atrophy four years after twelfth nerve-splitting.

Figure 2

(A and *B)* Successful eye closure. *(C* and *D)* Voluntary motion. *(E* and *F)* Symmetric facial tone at rest. (B.A., patient on left; H.M. on right)

TABLE 2
SUMMARY OF CASES WITH REGARD TO TONGUE FUNCTION RESULTS

Case		Hypoglossal Nerve Reconstruction Technic	Clinical (Atrophy)	Electrical Testing
1	A.R.	N.S.	Minimal	Not tested
2	M.D.	N.S.	Minimal	Excellent reinnervation
3	B.A.	None	Minimal	Excellent reinnervation
4	B.J.	None	Marked	Not tested
5	J.B.	D-H	No follow-up	Not tested
6	E.G.	N.S.	No follow-up	Not tested
7	H.M.	D-H	Marked	No reinnervation
8	M.M.	D-H	None	Excellent reinnervation
9	J.W.	N.S.	Minimal	Partial reinnervation
10	V.L.	D-H	Minimal	Excellent reinnervation
11	H.P.	None	Marked	No reinnervation
12	L.S.	None	Minimal	Partial reinnervation
13	B.Q.	D-H	Marked	Early reinnervation
14	F.S.	None	Marked	Early reinnervation

N.S. = Nerve splitting technic. None = No reconstruction of hypoglossal nerve.
D-H = Descendens-hypoglossal anastomosis.

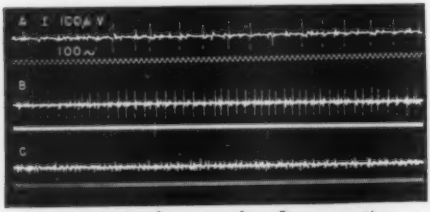

Fig. 3. F.S., four months after operation. No twelfth nerve reconstruction. *(A)* Motor unit discharges from orbicularis oris inferior with volition. *(B)* Slower recording of the same muscle. *(C)* Voluntary contraction of the left side of tongue. Small but numerous units were recorded.

cellent function; the fourth patient (E. G.) could not be traced.

Of the 5 patients without any attempt at restoration of lingual reinnervation, hemiatrophy is marked in 3 patients (B.J., H.P., and F.S.), although no gross functional incapacity is apparent as to speech or management of food or fluids in the mouth. However, 2 (F.S. and H.P.) show early electromyographic evidence of lingual reinnervation (Figs. 3 and 7), and 2 others (B.A. and L.S.) show only minimal atrophy with little or no deviation. Motion is preserved. Electrical tests confirm clinical evidence of neurotization (Fig. 5).

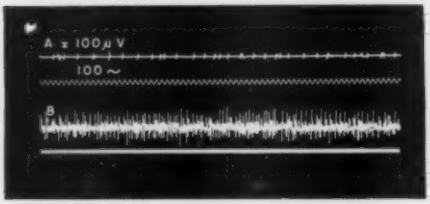

Fig. 4. L.S., seven months after operation. *(A)* Spontaneous fibrillations of denervation still present (orbicularis oris inferior). *(B)* The same muscle with volition; good firing of motor units

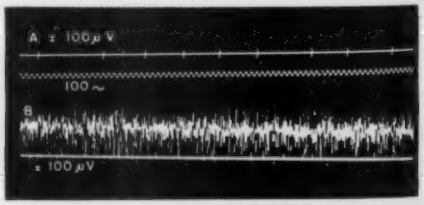

Fig. 5. L.S., seven months after operation (right side of tongue). No twelfth nerve reconstruction. *(A)* Spontaneous fibrillation potentials of denervation. *(B)* Large amounts of motor unit discharges with volition

DISCUSSION

Hypoglossal-facial nerve crossing frequently invites skepticism[5,6] because of its failure to reproduce mimetic responses and forehead wrinkling and because of interference with tongue function or associated movements.

While we agree that complete mimetic function is not restored,[7–9] we have noted that patients able to compensate for this deficit by limiting the breadth of their smile (Fig. 1C) can smile broadly after daily mirror practice (Fig. 1D). Poor eyebrow and forehead function was noted in our patients, as in others;[7,9] however, asymmetric eyebrow levels do not give an unattractive appearance.

The function of the tongue in distinct speech and effective swallowing has initially been impaired in our patients to some degree, but in a short time this limitation has become negligible.[10] None of our patients has noticed any disturbing movements of the face associated with use of the tongue. We find it particularly interesting that 3 patients with no twelfth nerve reconstruction show some positive electrical response in the ipsilateral side of the tongue. In this respect, McKenzie and Alexander[11] reported one instance in which no visible lingual atrophy was seen after section of 1 hypoglossal nerve—perhaps because of overlapping innervation from the normal twelfth nerve or outgrowth of normal motor neurons with reinnervation of affected neighborhood muscle fibers.[12–16]

Obviously, nerve anastomosis or crossing should be performed as promptly as possible. However, in some patients, in whom facial palsy may not be complete or permanent, nerve surgery should possibly be withheld for weeks or, occasionally, months. Despite such delays, hypoglossal-facial nerve crossings have proved successful. To our knowledge, the longest interval with successful outcome is two and one-half years,[11,17] although, in facial transplant surgery, R. Martin[9] reported "18–26 follow-ups of seven patients," claiming, "those done under one year had the best outcome."

Because some flicker of electrical stimulation was obtainable, operation was delayed, in 2 of our patients for fifteen and twenty-one months respectively, after removal of acoustic tumors. We now feel that these delays were unwarranted. For example, patient M.M.,

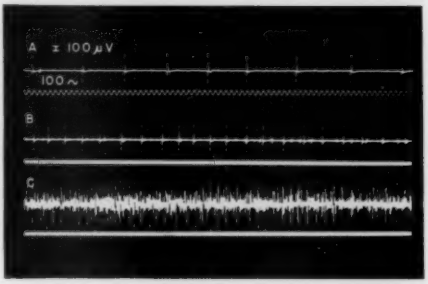

Fig. 6. H.P., eight months after operation. *(A* and *B)* Single motor unit discharges with volition (orbicularis oris inferior). In *(A)*, recording was faster for better details. *(C)* With stronger contraction, larger amounts of electrical potentials are recorded.

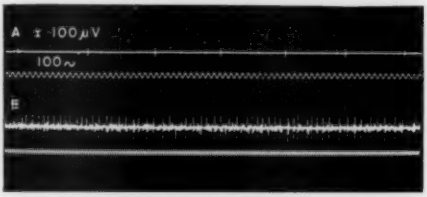

Fig. 7. H.P., eight months after operation (left side of tongue). No twelfth nerve reconstruction. *(A)* Fibrillation potentials of denervation at rest. *(B)* Firing of motor units with volition

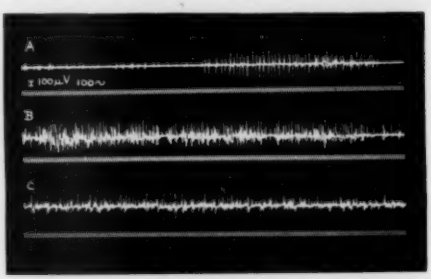

Fig. 8. V.L., eleven months after operation. *(A)* Orbicularis oculi inferior. Fairly strong motor unit discharges on blinking. *(B)* Orbicularis oris inferior. Large amount of motor unit discharges on voluntary contraction. *(C)* Right side of tongue after anastomosis of descendens hypoglossi to stump of twelfth nerve showing discharges on volition

delayed for twenty-one months, had a poor result when examined twenty-nine months postoperatively, although the other (V.L.), delayed for fifteen months, had excellent recovery of facial motor function as tested eleven months after nerve operation. In the first of these 2 patients, although delay cannot necessarily be held accountable for the failure, nothing was gained by the postponement. In the second, the patient was made to wait, with a paralyzed and unattractive face, perhaps one year longer than necessary. We delayed because changes in electrical excitability of the orbicularis oris and quadratus labii muscles seemed consistent with some neurotization. Later, we realized that the orbicularis oris had some nerve supply from the opposite facial nerve, as is often found in cases of Bell's palsy.

Now, even if there were changes in excitability suggestive of reinnervation and confined to only one or two muscles, we should not delay operation longer than six to nine months; with such minimal and static changes, the amount of good neurotization to be expected is small and quite inferior to the good results generally obtained with nerve crossing. Even with recovery in extreme cases of Bell's palsy, return of all individualized muscle function is not to be expected.[7,8]

We agree, therefore, that early repair is generally preferable, but that, if delayed, the outlook may not necessarily be hopeless. After about one hundred days, the cut nerve degenerates, forming a protoplasmic syncytium within the nerve sheath[18] which can serve as an excellent directional guide for growing fibers. The only problem for recovery, then, is the condition of the facial musculature, and this is extremely unpredictable. With electrical testing, we have seen, in 2 patients, evidence of a significant amount of denervated muscle fibers still present seven and eight years after total facial nerve severance. For this reason, careful electrical evaluation should be made before a hopeless prognosis is given.

In examining all the factors in the 3 patients who had poor results, no single reason for failure is apparent; 1 had operation three weeks after paralysis; 1, eight and one-half and 1, twenty-one months after paralysis. Apparently, failure of the repair cannot be specifically related to the time factor, as early repair does not always guarantee nerve regeneration, nor does inadvertent delay mitigate against good recovery. Recovery, when achieved, has been joyously and gratefully acknowledged by the patients; and none has complained of tongue deficits which are accepted in preference to total facial paralysis.

Addendum: Since completion of this paper, 3 other patients with successful hypoglossal-facial anastomosis have been seen four months after operation—making a total of 14 successful results in 17 patients. In only 1 patient was operation a complete failure.

SUMMARY AND CONCLUSIONS

1] Hypoglossal-facial nerve anastomosis was done in 14 patients with unilateral facial paralysis one to twenty-one months after onset.

2] Of the 14 patients, 11 had successful results at operation.

3] Retention of hypoglossal function by preserving some of the hypoglossal nerve through nerve splitting and/or by suturing the descendens hypoglossi to the cut distal end of the hypoglossal nerve resulted in considerable return of tongue innervation in most of these patients. No patient complained of incapacity in speech or swallowing or of disturbing, abnormal associated facial movements.

4] Electromyography indicates partial innervation of the hemiatrophied tongue without substitute nerve crossing.

5] The value of electrical studies before surgery and for postoperative evaluation and prognosis is noted.

6] The time interval between facial paralysis and successful hypoglossal-facial nerve crossing is discussed with reference to the condition of the facial musculature evaluated by electrical studies.

The authors wish to thank Dr. John E. Scarff and Dr. Joseph Ransohoff, members of the attending staff of The Neurological Institute, Presbyterian Hospital, New York, for permission to include their cases in this article.

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Requests for reprints should be directed to:
J. Laurence Pool, M.D.
710 West 168th Street
New York City 32

Electroencephalographic activation with combined Sodium Amytal and Metrazol

Gilbert S. Ross, M.D., and Frank Morrell, M.D.

THE USE of Metrazol for the activation of the electroencephalogram was developed approximately ten years ago. The aim of such early investigators as Cure, Rasmussen, and Jasper[1] was to gather information in cases of known epilepsy. Since that time, many investigators have also used this drug in differential diagnosis in cases of questionable epilepsy, unexplained syncopal attacks, and so on. Ducaud,[2] for example, states that Metrazol is useful in separating functional cases from cases of epilepsy. Buchtal and Lennox[3] state that Metrazol can be used to find "latent or silent neurological disorders." In this study, we have used Metrazol to obtain further information in cases of known epilepsy—not as a diagnostic tool.

The incidence of clinical seizures activated by the use of Metrazol is reported as ranging from 3[4] to 26%[5] in groups of known epileptic patients. The majority of physicians using Metrazol try to avoid this clinical effect and consider it unwelcome and disturbing.[6] On the other hand, Gastaut[7] states that a seizure must be induced in any patient considered for operation. The Metrazol-induced seizure pattern correlates with the noninduced clinical seizures in 80% of the cases cited by Ajmone-Marsan and Ralston.[6] These authors also state that in 50 patients with history of aura, 76% had reproduction of aura during Metrazol activation.[6]

In the University of Minnesota Hospitals' series of patients subjected to surgical excision of focal epileptic lesions, the observations—both clinical and electrographic—of the habitual seizure have been found to be of considerable clinical importance. When a complete and consistent seizure description is not available, a seizure is induced under controlled conditions by pharmacologic means. However, occurrence of a generalized seizure in the conscious patient should be avoided, especially in those patients who have not previously had a generalized seizure.

In order to prevent a major convulsion, the patients were first put to sleep with intravenous Sodium Amytal. Selection of this drug was prompted by studies in animals with chronic epileptogenic lesions.[8] Barbiturates administered to these animals were found to produce, within the first hour, minimal suppression of the primary focus, effective limitation of spread to basal structures, and good protection against Metrazol shock. Shimizu, Refsum, and Gibbs[9] have also demonstrated suppression of propagated seizure discharges by Nembutal. It was thought that combined use of barbiturate and Metrazol might significantly increase the patients' threshold to Metrazol and, by permitting a larger total dose of the drug, might broaden the range between the amount of Metrazol required to excite the focus and the amount needed to induce a generalized seizure. In addition, should a generalized seizure occur, the barbiturate premedication might reduce severity and duration of seizure and render the patient unaware of its occurrence.

MATERIALS AND METHODS

This study includes 14 patients. All were being considered for operation for epilepsy. They were 6 to 51 years old.

A routine electroencephalogram was done using unipolar and bipolar recording; then, an intravenous solution of 5% dextrose in water

From the division of Neurology, University of Minnesota Medical School, Minneapolis.
Supported in part by grants from the Teagle Foundation and by USPHS (B1158).

TABLE 1
SUMMARY OF ACTIVATION PROCEDURES AND DIRECT BRAIN RECORDINGS

Case	*Spontaneous*	*Sleep (Oral Seconal)*	*Metrazol*	*Photic*	*Amytal-Metrazol*	*Corticogram or deep electrode placement*
1	+	—	—	—	+	—
2	+	—	—	—	+	—
3	+	+	+	—	+	+
4	+	+	+	+	+	+
5	+	+	—	—	+	—
6	+	+	+	+	+	+
7	+	+	+	—	+	+
8	+	+	—	—	+	+
9	+	+	+	—	+	+
10	+	+	+	—	+	+
11	+	+	—	—	+	—
12	+	+	+	—	+	+
13	+	+	+	—	+	+
14	+	+	+	+	+	—

was started in one arm. Sodium Amytal was injected into the tubing in amounts sufficient to induce moderate to deep sleep, as manifested both clinically and on the electroencephalogram. Amounts used are listed in Table 2.

After the patient was asleep, the electroencephalogram was run for several minutes. Metrazol was then injected into the tubing at the rate of 100 mg. per thirty seconds. Amounts used are listed in Table 2; average dose was 1,520 mg. The end point of the Metrazol injection was determined by the changes noted in the electroencephalogram and in the status of the patient. If no changes were noted, the injection was continued up to 3000 mg.

TABLE 2
AMOUNTS OF AMYTAL AND METRAZOL USED

Case	*Age (years)*	*Sodium Amytal (mg.)*	*Metrazol (mg.)*
1	15	675	1,400
2	47	675	1,300
3	23	675	3,000
4	51	675	1,000
5	6	120	200
		675	800
6	26	675	2,000
7	19	780	2,000
8	45	540	2,500
9	24	1,560	400
10	27	675	500
11	13	720	0
12	30	450	800
13	24	450	1,300
14	32	450	700

RESULTS: PART 1

According to Merlis, Grossman, and Henriksen[5] and others, 350 to 500 mg. of Metrazol is the amount which will produce a generalized seizure in healthy subjects. Leffman and Perlo[10] have used up to 600 mg. We considered 500 mg. as the upper limit of safety. In this study, 3 patients received 500 mg. of Metrazol or less, while 11 patients received an average of 1,500 mg. of Metrazol or 3 times the amount we considered to be safe when administered without Sodium Amytal premedication. In other words, 11 patients had threshold to Metrazol raised by this technic. Despite this increase in Metrazol dosage, only 1 patient, Case

TABLE 3
INCIDENCE OF NEW ELECTRO-ENCEPHALOGRAPHIC FOCI ACTIVATED BY AMYTAL-METRAZOL TECHNIQUE

Case	*New foci activated*	*Correlation of new foci with corticogram or deep electrode placement*
1	Yes	Not done
2	Yes	Not done
3	Yes	Yes
4	Yes	Yes
5	Yes	Not done
6	No	
7	No	
8	Yes	Yes
9	Yes	Yes
10	No	
11	No	Not done
12	Yes	Yes
13	Yes	Yes
14	Yes	Not done

1, had a generalized tonic-clonic seizure. The patient was unaware of the seizure, which lasted several minutes. It is interesting that this seizure was related to the patient's habitual seizure, which was described as generalized shivering leading to severe clonic movements of upper extremities for three to four minutes. On the other hand, 5 patients had focal seizures produced by the Amytal-Metrazol technic – Cases 5, 6, 12, 13, and 14. In 3 of these patients, the induced seizures correlated with the clinical history of the patients' seizures – Cases 6, 12, and 13. In Case 6, for example, the patient's clinical history was that of an aura of eructation and flatus with flushing of the face, followed by adversion of the head and eyes to the right, and, then, by generalized convulsion. With the Amytal-Metrazol activation, the seizure was characterized by opening of the eyes, staring for a few seconds, then turning head and eyes to the right with flexion of the right arm. This same seizure was also activated by Metrazol alone but was followed by a generalized convulsion.

In summary, the Amytal-Metrazol technic increased threshold to Metrazol. An average of 1,520 mg. of Metrazol was received by 11 patients. Of 14 patients receiving the Amytal-Metrazol activation, only 1 had a generalized seizure and he was unaware of it. In the 9 patients who received Metrazol activation without premedication, 2 had generalized convulsions of which they were aware.

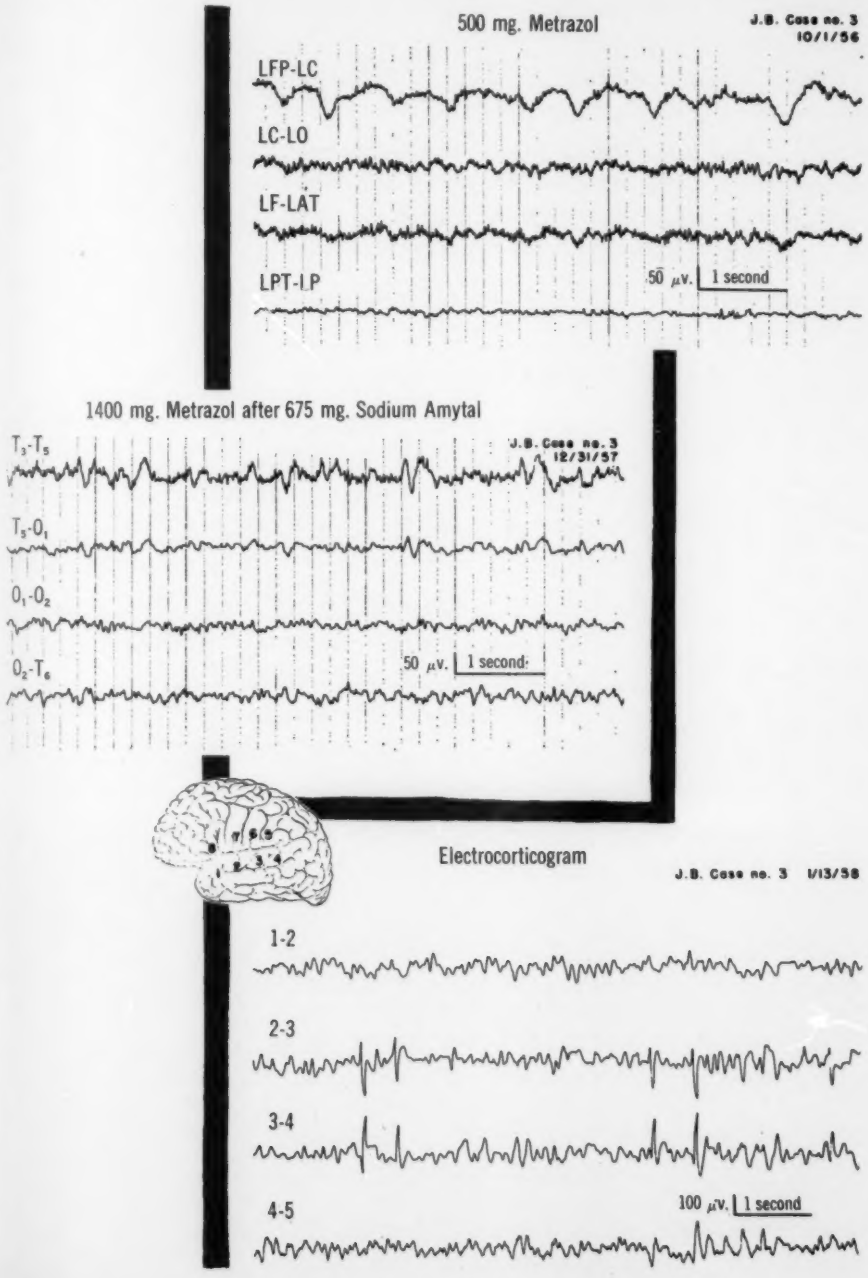
In using Metrazol alone, our intent had been to produce only activation of the electrographic focus, *not* a clinical seizure. When using Amytal-Metrazol, our intent had been to reproduce the habitual seizure in order to study its pattern.

PART 2

Of the 14 patients studied, 10 revealed electroencephalographic foci under the Amytal-Metrazol technic which were not seen by previous activation technics. In 6 of these – Cases 3, 4, 8, 9, 12, and 13 – electrocorticograms or deep electrode placement were carried out. In all 6 of these patients, correlation existed between the foci as demonstrated by the Amytal-Metrazol technic and the electrocorticograms and depth electrode recordings. Case 3, for example, had a left midtemporal spike focus demonstrated for the first time by the Amytal-Metrazol technic. Electrocorticogram revealed a high voltage spike in the midportion of the superior temporal gyrus (Fig. 1). In Case 13, the Amytal-Metrazol technic revealed a right temporal discharge synchronous with central vertex discharge. Electrode implants in the right temporal lobe in the region of the uncinate gyrus and midline thalamus revealed a thalamic discharge being triggered by an irritative focus in the right temporal lobe.

Of the 4 patients who had new foci demonstrated by the Amytal-Metrazol technic, but who did not have electrocorticograms, 2 (Cases 1, 2) did not have any previous activation procedures for comparison. In Case 5, the foci demonstrated by the Amytal-Metrazol technic correlated with localization as determined by history of clinical seizure. In this

(Opposite page) Comparison of the electroencephalographic records under Metrazol and Amytal-Metrazol with the electrocorticogram. The left midtemporal spike focus is demonstrated in Tracing 2 and is confirmed by a similar discharge from the midportion of the superior temporal gyrus as seen in Tracing 3. Eye movement artifact is present in the upper tracing.


500 mg. Metrazol
J.B. Case no. 3
10/1/56
LFP-LC
LC-LO
LF-LAT
LPT-LP
50 μv.
1 second
1400 mg. Metrazol after 675 mg. Sodium Amytal
J.B. Case no. 3
12/31/57
T3-T5
T5-O1
O1-O2
O2-T6
50 μv.
1 second
Electrocorticogram
J.B. Case no. 3 1/13/58
1-2
2-3
3-4
4-5
100 μv.
1 second

patient, Amytal-Metrazol activated focal spikes in the right frontotemporal and left temporal areas along with slow waves in the left frontal area. The clinical seizure was described as beginning with eye pain followed by twitching of the left side of the mouth and, then, slow automatic movements of the left arm. These movements also occurred on the right side. On several occasions, the patient had speech difficulty lasting several hours after the seizure. In Case 14, the new electroencephalographic foci found by the Amytal-Metrazol technic were demonstrated in the pharyngeal electrodes, which had not been used previously in the sleep or the usual Metrazol activations. It is therefore difficult to know whether these foci would have been apparent before the Amytal-Metrazol was used if nasopharyngeal recordings had been done.

In 4 patients, no new electroencephalographic foci were activated by the Amytal-Metrazol technic. In 2, (Cases 6, 7), evaluation of the patient was made more complex. For example, the Amytal-Metrazol technic in Case 6 activated bilaterally synchronous seizure discharges after the previous records had demonstrated focal abnormalities. These focal discharges were later verified by the electrocorticogram. In Case 7, the Amytal-Metrazol method did not activate a right temporal focus which had been found previously and was later verified by the electrocorticogram. In the remaining 2 patients (Cases 10, 11), the Amytal-Metrazol method did not add any further information to that which was already known through use of previous activation technics.

In summary, 10 out of 14 cases activated by the Amytal-Metrazol technic showed electroencephalographic foci not already demonstrated by previous activation studies. Of these 10 patients, 6 had electrocorticograms or depth electrode recordings which correlated with the foci activated by the new technic.

PART 3

After the patients were put to sleep with intravenous Sodium Amytal, several minutes of electroencephalographic recording were taken. Originally, the Sodium Amytal had not been intended to produce separate sleep activation, and, therefore, these sleep records were not as complete as were the routine Seconal sleep recordings in number of different runs performed or in amount of record obtained. However, as an afterthought, these sleep recordings were compared to the routine sleep recordings taken after oral Seconal had been given. Our purpose was to determine the amount of information obtainable from the sleep recording which was the first step in the Amytal-Metrazol technic.

Eleven patients had previous routine sleep activation with oral Seconal; 1 patient had a routine sleep record produced by 390 mg. of intravenous Sodium Amytal; 11 of these 12 patients also had sleep recordings from intravenous Sodium Amytal as the first part of the Amytal-Metrazol technic. Of these 11 patients, 8 had intravenous Sodium Amytal sleep recordings which demonstrated either an equal amount of information or more information – as verified by Metrazol activation or electrocorticogram – than obtained by the routine oral Seconal method – Cases 4, 5, 6, 7, 9, 10, 11, and 12. In Case 9, for example, the oral Seconal sleep record revealed epileptiform discharge in the left hemisphere which was reflected in the right hemisphere. A spike focus in the left nasopharyngeal electrode was seen. The intravenous Amytal sleep recording revealed left frontopolar and left frontotemporal spike foci. The electrocorticogram revealed independent active spikes in the left mid- and posterior temporal areas, as well as in Broca's area.

In 8 of the 11 patients for whom we have both oral Seconal and intravenous Sodium Amytal sleep recordings, the intravenous recording revealed an equal amount of, or more information than, the routine oral method.

PART 4: COMPLICATIONS

In 4 patients, Cases 5, 7, 9, and 11, from 6 to 24 years old, injection of Metrazol produced a sudden arousal of the sleeping patient. The arousal, however, was incomplete and consisted of abrupt eye opening and pupillary dilation, thrashing about, pulling at the intravenous apparatus, and attempts to sit up. The patient remained unresponsive to commands. In 3 of 4 patients, the procedure was continued, although with moderate difficulty, and was concluded satisfactorily.

TABLE 4
SEIZURES INDUCED BY METRAZOL AND AMYTAL-METRAZOL

Case	*Clinical focal seizure produced* by Metrazol	by Amytal-Metrazol	*Clinical generalized seizure produced* by Metrazol	by Amytal-Metrazol	*Correlation of activated seizures with clinical seizures*
1	Not done	No	Not done	Yes	Yes
2	Not done	No	Not done	No	No seizures activated
3	No	No	No	No	No seizures activated
4	No	No	No	No	No seizures activated
5	Not done	Yes	Not done	No	No
6	Yes	Yes	Yes	No	Yes
7	Yes	No	Yes	No	Yes
8	Not done	No	Not done	No	No seizures activated
9	No	No	No	No	No seizures activated
10	No	No	No	No	No seizures activated
11	Not done	No	Not done	No	No seizures activated
12	No	Yes	No	No	Yes
13	No	Yes	No	No	Yes
14	Yes	Yes	No	No	No

In Case 11 (aged 13), injection of any appreciable amount of Metrazol after the initial arousal was impossible. The patient developed extreme rage reaction which included efforts to bite the examiners each time a further injection of about 0.1 cc. was attempted. Between such injections, the patient subsided into moderately deep sleep. Finally, the procedure was discontinued and the patient returned to the ward. No significant drop in blood pressure occurred, but pulse rate decreased from 80 to 60 per minute; the patient slept for eight hours and had urinary retention. On awakening, he was oriented, responsive, and voided spontaneously.

Such prolonged sleep has not occurred in any patient in whom the full procedure was carried out. It would seem wise, therefore, when impossible to continue Metrazol injection, to administer an analeptic—such as amphetamine—intramuscularly before returning the patient to the ward.*

DISCUSSION

Based on the results described above, the Amytal-Metrazol technic may be useful in certain clinical situations. First, with patients in whom a Metrazol study is contemplated, this technic will raise the Metrazol threshold and decrease the risk of a generalized seizure. Discharging foci are brought into sharp relief and are not obscured by muscle artifact – which is often the case when Metrazol is used without barbiturate premedication. At the same time, a sleep recording can be obtained with the Sodium Amytal which may give further information without additional cost to the patient or additional scheduling with the electroencephalographic laboratory for oral Seconal sleep recordings. Second, the technic is of distinct value in those patients in whom observation of a clinical seizure is important, provided, of course, that the seizure components of interest are not of a purely sensory or subjective character. Third, the technic is valuable in

*In 2 patients studied subsequent to the initial investigation, a similar arousal response occurred and made it impossible to administer Metrazol in any significant amounts. Both these patients had moderate to severe drop in blood pressure on return to the ward (90/60 and 70/50). Elevating the foot of the bed was sufficient to restore normal levels within ninety minutes. No pressor agents were used. Such a response to large doses of Sodium Amytal is, of course, not unexpected. However, this response underscores the need to administer analeptic or pressor agents in the event that administration of Metrazol cannot be completed. The fact that no hypotension has occurred in any patient in whom the full procedure was done suggests that Metrazol is an effective antagonist to the ganglionic blockade produced by amobarbital. Future studies might explore the possibility of using a short-acting barbiturate which exhibits less depression of autonomic ganglia.

patients who are being considered for surgical excision of focal epileptic lesions. Clear delineation is permitted of the less active, but independent, foci which may contraindicate surgery and be obscured by bilateral discharge in the usual Metrazol activation.

At the present time, we have no explanation for the difficulties encountered in the younger age group. Case 11, previously described, had a history of severe behavior disorder – physical violence inflicted on other children, temper tantrums, and paroxysmal episodes of rage. A convulsive disorder was suspected. A previous sleep recording revealed bilateral rhythmic frontal spikes. The difficulties which the patient experienced after administration of Sodium Amytal and Metrazol may have been a reproduction of his clinical behavior. The electroencephalogram was obscured by muscle and movement artifact, so that during the injections no abnormalities were visible on the recording.

SUMMARY

To study a technic for the activation of the electroencephalogram by the combined use of Sodium Amytal and Metrazol, 14 patients were selected.

The Amytal-Metrazol technic increased the threshold to Metrazol in 11 patients, broadening the range betwen the dose of Metrazol required to excite a focus and that which produced a generalized seizure.

In 10 out of 14 patients, electroencephalographic foci were revealed which had not been demonstrated by previous activation studies.

In 8 out of 11 patients for whom we have both oral Seconal and intravenous Sodium Amytal sleep recordings, the intravenous sleep recording revealed an equal amount of, or more information than, the routine oral method.

Possible clinical uses of the technic are discussed, as are the complications encountered during the procedure.

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E. P. Richardson, Jr., M.D., *Section Editor*

Presented by J. Park Biehl, M.D., and Joseph Smith, M.D.

Case presentation. A 40-year-old woman was first admitted to the hospital on March 24, 1943, because of twitching of the left arm and leg. On March 4, while working in the kitchen, she suddenly fell to the floor unconscious. She estimated that she remained so for about forty-five minutes before awakening with the dog licking her hands and face. Though she felt very weak, she managed to telephone a neighbor, after which she went to bed. Her physician told her that she had had a stroke; the left side of her face was paralyzed, and her speech was indistinct. She was generally weak, but there was no local paralysis of any of the extremities. After about a week in bed, she developed fever and a cough and was told that she had pneumonia. She was treated at home. She was recovering from this nicely and was up in a chair. At about noon on March 14, 1943, she noted a slight headache and was aware that her left hand was twitching and jerking. This gradually progressed over the next few days until it became apparent that her entire left upper extremity and, to a lesser extent, the left lower extremity were involved in gross twisting, writhing, flinging movements, which she characterized as nerve-wracking and unrelenting. At no time was the face noted to be involved in this process; indeed, the facial weakness had improved remarkably. Her speech had become distinct. There was no nausea, vomiting, or disturbance of vision. A review of her history revealed a cholecystectomy in 1938 and a total hysterectomy and appendectomy in 1940.

On admission to the hospital, her blood pressure was 130/78; temperature normal, pulse rate 112, and respiratory rate 24. General physical examination was not remarkable. She was right-handed. The significant neurologic finding was persistent involuntary movements of the left extremities. It was noted that the left limbs would jerk violently in sudden gross movement and spasmodic twisting. There was also some similar purposeless movement of the right lower extremity, of which the patient was little aware, and infrequent gross movements and smaller movements of the right foot and toes. These movements would interrupt efforts at purposeful activity. Tests of coordination were poorly performed with the left extremities. There was some reduction in strength on the left. The patient attempted to quiet the involuntary movements by holding onto the side rail of the bed or by holding the left arm with the right hand and by lying on the left arm. It was believed that touch, pain, temperature, and vibration were adequately perceived.

The optic disks and vessels were normal; visual fields were thought to be normal. The pupils were 6 mm. in diameter and reacted promptly and through a fair range to light. The corneal reflexes were brisk and equal. There was weakness of voluntary and emotional movement of the left lower portion of

From the Cincinnati General Hospital.

the face. Hearing was normal. The soft palate elevated in the midline. The tongue protruded in the midline and was quickly withdrawn. Deep reflexes were 2+ and equal throughout. The left plantar response could not be obtained; the right was flexor.

Routine laboratory studies at this time were normal. The initial pressure in the cerebrospinal fluid was 110 mm. of cerebrospinal fluid. There were 10 lymphocytes and 1 red blood cell per cubic millimeter; total protein was 36 mg. per cent. The Wassermann and colloidal gold reactions were negative. Blood Wassermann was also negative.

It was noted on the first hospital night that there were no movements during sleep, an observation made on several occasions. Over the next several days, the involuntary movements of the limbs diminished.

On April 2, 1943, when she was reexamined by a neurologic consultant, she was restless and rolled her head from side to side, making repetitive smacking movements of the lips. He termed the restlessness as choreiform. He noted occasional involuntary movements of an entire left limb that were writhing and suddenly interrupted by small twitches of the fingers or toes and inversion of the limb. There was hyperextension at the metacarpophalangeal joints when the left hand was outstretched (Warner hand). He noted a pronator sign of the outstretched left upper extremity. Tonus was reduced in the left extremities. All deep reflexes were hyperactive; the left great toe was held in constant dorsiflexion. Gentle plantar stimulation on the left elicited nothing; to a deeper stimulus, she withdrew the whole limb. The left lower facial weakness was obvious, and she protruded her tongue and maintained it there.

She was discharged on April 3 and seen again in the Neurological Clinic in May 1943. At this time, a slight left emotional facial weakness was still present. Voluntary movement was well performed, and there were no involuntary movements or weakness of the limbs. Reflexes were normal.

Shortly after her clinic visit in May, she noted pain under the symphysis pubis and had some difficulty starting the urinary stream. Other than this, she had no particular complaints. The blood pressure was 160/94. Deep reflexes were more active on the right side; there were no abnormal reflexes. Some observers thought that she had an equivocal extensor plantar response on the right. Lumbar puncture at this time revealed an initial pressure of 75 mm. of cerebrospinal fluid; there were 1 lymphocyte and 30 red blood cells per cubic millimeter; total protein was 50 mg. per cent. Wassermann and gold curve reactions were again normal.

Cystometric study revealed a first desire to void at 100 cc. with pain; further distention of the bladder caused almost continuous pain. In attempting to void with the catheter in place, there was a sudden rise in intravesical pressure followed by a slow, step-like fall to the previous level. There was marked accentuation of pain with this attempt. After removal of the catheter, she was unable to void until put in a tub of lukewarm water. It was not thought that this represented evidence of neurogenic dysfunction.

She was seen in September 1943 by a psychiatric consultant, who noted inappropriate emotional responses, defects of retention and recall, and impairment of calculation. The patient expressed hopelessness and occasional suicidal ideas. The consultant did not feel she was psychotic. She improved but constantly suffered from urinary frequency and pain.

In January 1944, she was seen by a neurologic consultant who noted that, since discharge from the hospital, she had 3 or 4 attacks, the description of which sounded something like convulsions. The patient said that she became unconscious momentarily, shook, tried to grab at things about her, and drooled saliva. Shaking occurred in one or the other hand. In addition, it was noted that she was complaining of pain in the bladder, which she said was due to nerves. Blood pressure was 192/108. There was some arterial narrowing of the retinal vessels, slight arteriovenous compression, and obvious left lower facial weakness. The right pupil was a shade smaller than the left; both reacted promptly. Sensation was intact, and speech was normal. The outstretched left hand assumed a marked Warner attitude. There was no muscle weakness. Coordination was good. Finger and toe wriggling was done well on both sides. Sensation was intact.

She was next seen on November 5, 1951, at which time she was 48 years of age. On that morning, her husband had found her unconscious with white phlegm drooling from the side of her mouth. There was sharp jerking of her right arm, lasting but a few moments. She got out of bed, but, a few moments later, was found unconscious in the bathroom, again jerking on the right side. The jerking subsided in about fifteen minutes, but she remained unconscious.

Upon reaching the hospital, she was conscious. Her speech was clear, but she was confused and disoriented. Her visual fields were full to confrontation testing. No weakness was made out. The deep reflexes were 3+ throughout; the plantar responses were flexor on repeated examinations. Sensation was apparently intact. Blood pressure was 170/115. When able to communicate better, she complained of frontal headache. Lumbar puncture revealed an initial pressure of 205 mm. of cerebrospinal fluid. There were 70 red blood cells per cubic millimeter and a total protein determination of 52 mg. per cent. Other studies of the cerebrospinal fluid were within normal limits. Blood urea nitrogen was 23 mg. per cent; fasting blood sugar 74 mg. per cent. Roentgen studies of the skull and chest were reported normal. An electroencephalogram revealed a left anterior focus in an otherwise generally well-ordered record, with a slow, 4- to 6-per-second focal pattern.

On November 19, a pneumoencephalogram was recorded as follows: the air did not completely outline the ventricular system; there was considerable air in a localized area over the right posterior parietal region where the sulci were considered to be dilated; and there was a good deal of air present in the subdural spaces over the frontal poles and beneath the tentorium. It could be determined that there was no shift of the ventricular system.

She was discharged on November 26 and was not seen again until October 7, 1955. During the interval, she had been taking Dilantin and phenobarbital. She had been admitted to another hospital in August 1955 because of anorexia and weight loss. About three weeks earlier, she had lost control of bowel and bladder. In early October, she became progressively weaker, disoriented, and stuporous.

On October 7, she was found to have dilated, equal pupils which reacted to light. The fundi showed old exudates, arteriovenous nicking, tortuosity, and silver wiring. There was no papilledema. There was voluntary resistance to passive movement of all extremities. Deep reflexes were 3+ throughout. There was a right Hoffmann sign. The abdominal skin reflexes were absent, and the plantar responses were flexor bilaterally. She moved all extremities in response to painful stimuli, but no other sensory evaluation was made. The blood urea nitrogen was 94 mg. per cent, and her blood pressure was 180/84. She was dehydrated and dyspneic, and there were many rales in the chest and marked enlargement of the heart. The cerebrospinal fluid examination was normal. She was treated in an emergency fashion and suddenly developed pulmonary edema and hematemesis. She died at 5:30 A.M. on October 11, 1955.

Differential Diagnosis

DR. J. PARKE BIEHL: If we could begin in the middle of this case, it would be fairly easy to speculate on the nature of the illness. We could begin at the point where hypertension became established and quite readily say that later events were on the basis of hypertension, perhaps on a renal basis; that the neurologic disorder was due to hypertensive brain disease; and that the patient died of uremia. But the few paragraphs that precede the description of the onset of the hypertensive disorder caused the larger amount of thought on my part in trying to interpret this case. The fact is that the stroke she had in 1943 occurred before she ever showed any evidence of cardiovascular disease. She was normotensive; she had a normal sized heart; and there is really no basis at all for making a diagnosis of a stroke on the basis of cerebrovascular disease in a 40-year-old woman.

I can reflect in passing that perhaps the ensuing difficulties – the massive brain damage which is implied by the protocol in the later stage of her illness – have obliterated the process that brought about this initial episode in 1943, and that even though I can't make a very good diagnosis of that episode, neither can Dr. Smith.

To begin then with the later symptoms, we

may consider first the bladder difficulty, which I find rather hard to analyze. In May 1943, the patient noted pain under the symphysis pubis and some difficulty in starting her stream. There was no other particular complaint. Her blood pressure was perhaps a little elevated at that time. There were essentially normal neurologic findings except for the red cells which I'll pass off as being due to trauma. She had a cystometric study. I don't know if this implies that she got a complete urologic work-up with urinalysis and pyelograms. I wonder especially if she had a urinalysis at that time which showed any abnormality. The cystometric study wasn't thought to be due to neurologic disease; this is a reassuring statement, and I tend to agree. I think that this type of finding is seen with cystitis, which would then imply urinary tract inflammation. We note that the blood pressure rose after this episode, and it seems rather reasonable to suspect that she had pyelonephritis at this time and that the blood pressure which thereafter was always elevated was a renal form of hypertension. This culminated years later with frank signs of severe hypertension, uremia, and what we will conclude ultimately is cerebrovascular disease on the basis of hypertension.

There are few other things that this patient could have had subsequent to 1943 which would explain this later phase of her illness. If we look through the protocol, we find that not much happened after 1943 until 1951. She saw a psychiatrist in 1943, but we don't know why. I think that knowing this might be important. We don't know how she really was feeling except that she was suffering from urinary pain and frequency. Her general condition and the intensity of the abnormalities might be significant. However, I am going to assume that these were not of much importance in making a final diagnosis.

She had attacks in 1944 that are not clear to me. I would be reluctant to call them fits, although they could have been. I am equally reluctant to call them strokes, although, by this time, at the age of 41 and with a fairly high blood pressure, it would not be inconceivable that these could represent the first in a series of cerebrovascular accidents which led to the state in which her brain was found at the time she came to autopsy.

In 1951, which was eight years after the attacks in 1944, she did have what appeared to be a real convulsion. At this time, she was unconscious, confused, and disoriented as a result of this fit; however, she became able to communicate later. There were no long tract signs. Her blood pressure was elevated, but there is no real organic damage implied by the occurrence of this fit except as shown by the pneumoencephalogram. I take this to indicate fairly extensive cerebral atrophy, that has occurred within the eight years after the onset of what we are supposing was renal hypertension. (For the ensuing four years, her medical status is again unknown.) She returned in 1955 with uremia, an obvious diagnosis on the basis of accelerated hypertension, dehydration, heart failure, enlargement of the heart, and terminal hematemesis. The symptoms leading up to this were also consistent with uremia – progressive weakness, disorientation, and stupor.

The portion of her illness considered so far, beginning with the renal disorder, can be called hypertension, probably renal, with cerebrovascular disease due to hypertension, and terminal uremia.

Turning to the beginning of the protocol, one finds the essential diagnostic difficulty. I can't logically fit the original stroke of 1943 in with any of these subsequent developments. Here is a woman of 40, who was first seen ten days after having had a sudden attack of unconsciousness. She had residual paralysis and dysphasia and ten days later began showing a peculiar and spectacular disorder of the left side of the body. All of this has occurred in the presence of no disease that we can put our finger on. She was normotensive at this time; her eye grounds were normal. Her heart was not enlarged; and there is no basis at all for suspecting vascular disease. This is a situation which has dissatisfied my diagnostic senses before. It dates back to a patient for whom I was caring as a house officer. A 32-year-old truck driver who was absolutely normal in other respects died with a stroke. This drove home the fact that cerebrovascular disease, that is, atherosclerosis with stroke, can indeed occur in such an individual. It was a very painful thing for me to realize. It is equally painful for me to make a diagnosis of

simple atherosclerosis and thrombosis in the brain of this apparently normal woman.

We might turn now to the localization of this lesion to see what help this might bring in arriving at a diagnosis. The lesion involves tracts serving the left side of the face and speech, a common combination, no doubt involving the inferior portion of the motor strip and the angular gyrus or the radiations thereof. The twisting, writhing, and flinging movements of one side of the body, described by the patient as nerve-wracking and unrelenting – no doubt exhausting and a source of great concern to the patient – are typical of what we call hemiballismus. This is the third of the hyperkinesias, the other 2 being chorea and athetosis. Hemiballismus is not particularly characterized by the nature of the motion as by its lateralization. If it were double hemiballismus, so to speak, I think it probable that most examiners would call it chorea or possibly choreoathetosis. There are those who would probably call this hemichorea in our patient and not be challenged in the matter. In any event, the flinging movements are the thing that characterizes the abnormality and really sets it aside from athetosis which is more writhing in character, the so-called mobile spasm. The movements are completely characteristic in their description. They did disappear during sleep, and this was probably the only relief that this woman had from this disorder. It is a disorder that one never forgets, having seen it once. We know that hemiballismus is commonly associated with a lesion in the contralateral subthalamic nucleus. It has been said that it is likely that any destructive process of this nucleus would produce hemiballismus and that this has repeatedly been demonstrated experimentally. Certainly, pathologically, the area and the movement are well associated. Hemiballismus usually occurs in the aged as the result of a stroke as we are hypothesizing here. Occasionally, cerebral metastasis localized in the subthalamic nucleus can cause hemiballismus. It's usually seen in old persons, and its importance is that it is extremely debilitating and exhausting. Because of this, it usually causes death in patients who would otherwise survive weeks or months, perhaps, and who usually ultimately work themselves to death, dying of exhaustion or heart failure. Characteristically, it is said to appear some time after the other manifestations of the stroke as in this case. Here it appeared ten days after the initial stroke.

Cases are on record, however, in which the lesion did not involve the subthalamic nucleus directly and rather involved connections of this nucleus with adjacent areas, usually in the basal ganglia. Lesions in the putamen and head of the caudate nucleus, which, as you recall, are included in the more anterior portion of the basal ganglia, have been described in patients showing hemiballismus by reliable investigators. If this were the case, we could assume that a single lesion exists in the capsule near the genu where the face and speech fibers descend, adjacent to the head of the caudate nucleus and the putamen. There a single lesion conceivably could produce combined hemiballismus with disorders of the face, all on the left.

This suggests that we are dealing with a deep lesion in the white matter of the brain in or about the basal ganglia. What could this mean? Vascular disease is again the first choice. I think that one might make a reference to multiple sclerosis. There is no basis here for multiple sclerosis in the early or the late stages of the disease since the clinical picture is not characteristic enough of this disorder. I think we are entitled to expect a certain amount of *characteristicness* in advanced cases of multiple sclerosis. While multiple sclerosis does involve the deep white matter such as this, I think it is impossible to consider it further.

The nature of the onset of this stroke with sudden ictus, unconsciousness, and gradual recovery again suggests the vascular nature of this initial episode. Aside from atherosclerosis with occlusion of a vessel, we might consider the possibility of an aneurysm; we know that aneurysms within the cerebral vessels usually do not occur deep within the tissues but rather in the subarachnoid space at the base of the brain. Certainly, hemorrhage from an aneurysm could dissect into the brain from the outside, but I think it would be rather unusual for such extensive dissection to occur in the course of cerebral aneurysms. This I don't think likely, although, when we see strokes in younger women without evidence of other vascular disease, aneurysm is a con-

sideration in the evaluation of the patient. An arteriovenous malformation could occur deep within the brain or the basal ganglia. I don't know how frequently one would expect to find such lesions in the region of the basal ganglia. Here the stroke could have been on the basis of some sudden vascular alteration within a malformation. Again, however, there is no real reason why one should consider this further. May we see the roentgen studies?

DR. HERBERT FRANCIS: The first roentgen examination was in November 1951. Skull films showed no gross abnormality. There was a small deposit of calcium in the region of the right carotid siphon. On a later film in 1955, evidence of vascular disease of the right internal carotid artery was again seen.

A pneumoencephalogram was made in November 1951. You will note that while the anterior portion of the right lateral ventricle is not too well filled, the occipital horn of the right lateral ventricle is dilated. There is also a bit more air over the cortical sulci than is seen normally. We see an essentially normal left lateral ventricle. The brow-down projection again shows the marked dilation of the occipital horn on the right side with essentially normal occipital horn on the left. There is some shift of the posterior portion of the ventricular system toward the right; however, on the brow-up projection (filling the anterior portion), there is no shift of the anterior portion of the ventricular system. In summary, we have evidence of vascular disease in the right internal carotid artery, localized cerebral atrophy in the right posterior parietal region, and generalized cerebral atrophy as evidenced by a little more than a normal amount of air over the sulci.

A chest film taken in 1951 shows no abnormality except for a fibrocalcific complex in the hilum, probably due to old tuberculosis. The lateral view of the abdomen in 1951 shows marked calcification of the abdominal aorta, again evidence of vascular disease.

DR. BIEHL: The diagnosis of atherosclerotic vascular disease is strengthened by the illustration of calcium in the cerebral vessels and in the aorta. It's too bad that the chest film was not a 6-foot projection. I guess we'll have to fall back on old-fashioned physical evidence that the heart was enlarged terminally, as described in the protocol. Is there any information about the urine in the chart?

DR. SAMUEL A. TRUFANT: Yes, we have a record of 2 urinalyses on her first admission; neither contained red cells, albumin, or sugar. The first specific gravity was 1.020; the second 1.005.

DR. BIEHL: What did the urine show when she had the bladder symptoms in May 1943?

DR. TRUFANT: Again the urine was completely normal.

DR. BIEHL: This still leaves me rather puzzled about the nature of this obvious urologic disorder, which is still characterized by inflammation, I'm sure. I am still rather inclined to think that it did represent pyelonephritis, even in spite of the recorded urinalyses.

In conclusion, I believe that the original episode was due to atherosclerosis. We shall probably see an old softening in the region of the basal ganglia on the right; marked cerebral atrophy, particularly on the right, probably with multiple other areas of softening deep within the brain; and cerebrovascular hyalinization due to hypertensive brain disease. I suspect that we'll see pyelonephritis and that this woman died of uremia due to chronic pyelonephritis and the effects of hypertension.

DR. CHARLES D. ARING: The students' diagnoses concurred with Dr. Biehl, with 34 students making a diagnosis of hypertensive encephalopathy or repeated small vascular accidents (thromboses of cerebral arteries); the vessel particularly mentioned was the striate. There were 4 dissensions from this diagnosis: 1 student thought that this might be Huntington's chorea, 1 that there might have been several episodes of cerebral embolism from old pelvic inflammation, and 2 couldn't arrive at a diagnosis — and I don't know that we can quarrel with them. Quite a number of the students in their written discussions put the main lesion in the corpus Luysii to account for the hemiballismus.

There was some diffidence in the student discussions about attempting localization, which I think was not quite warranted. The roentgen and electroencephalographic evidence might have been used in this regard, even though the evidence from neurologic examination was baffling. The term hemiballismus is

evidently not too well-known among you. Dr. Biehl explained this term satisfactorily. When we see wild, swinging movements of the limbs on one side, completely uncontrollable and moving around in all planes, we talk about ballismus.

Dr. Francis made one addition that we didn't have in the protocol. We hadn't heard nor had we read anywhere in the chart about calcific change in the internal carotid on one side in the 1951 films; this interpretation must be as a result of his restudy of the roentgen material.

STUDENT: In the protocol, it says that there were coarse, irregular movements on the left, but it describes some involuntary movements in the right foot. Can you call this hemiballismus when there is a slight involvement on the right side?

DR. ARING: Yes, I think you can.

STUDENT: What about the fact that the movement disappeared during sleep?

DR. ARING: All involuntary movements disappear during sleep. Sometimes, palatal myoclonus is said to continue during sleep; I've never seen this myself.

STUDENT: Dr. Aring, could you say something about the degree of relative shock following cerebrovascular accidents and how long shock will last?

DR. ARING: It depends on what it is and where it is; usually, not longer than a few hours.

DR. BIEHL: You're talking about cerebral shock?

DR. ARING: Yes, diaschisis.

DR. BIEHL: What about shock that includes a fall in blood pressure?

DR. TRUFANT: Whenever we see a patient with a stroke with very low blood pressure, we look for some other explanation for it.

DR. DANIEL OSHER: In rereading my notes in the chart in 1943, apparently I got the story that the process began with a right hemiparesis from which she recovered. She then developed left hemiballismus. In my examination, she had hyperactive reflexes on the right. When she was rid of the hemiballismus, she had some left facial weakness. This seems a rather confusing bilateral picture. In the air studies there seems to be biparietal atrophy, more marked on the right side. The question arises if she had some queer lesion such as a sagittal sinus thrombosis.

Pathologic Discussion

DR. JOSEPH SMITH: I'll do my best to produce a few significant scars from the burned out building. The body was that of a rather poorly nourished woman. An area of acute hemorrhagic erosion present at the cardiac end of the stomach explained the terminal hematemesis and the presence of coffee-ground content in the esophagus and stomach. Evidence of heart failure was conspicuous; there were large pleural effusions (2,500 cc. in each side) and ascites (3,500 cc.) as well as a congested liver and congested lungs. Microscopically, the lungs showed also some lobular pneumonia, heart failure macrophages in the alveoli, and a healed tuberculous lesion. The failure was associated with cardiovascular hypertrophy (430 gm.), the bulk of this being in the left ventricle and indicating hypertensive hypertrophy. There was, however, a healed rheumatic mitral lesion, but the degree of deformity of the valve was not great. Antemortem thrombi were not present in any cardiac chamber. The kidneys were unequal in size, the right weighing 135 gm. and the left 65 gm. In the smaller one, atrophied glomeruli and tubules were more marked than in the larger; in both, there were chronic inflammatory infiltrations between tubules, occasional groups of hypertrophied tubules, and marked arteriosclerosis. An organized thrombus or thromboembolus was present in an arcuate artery in the smaller kidney, and the broad scar adjacent to it could be attributed to vascular occlusion. On the whole, however, it was difficult to assess whether the bulk of the kidney destruction was on the basis of chronic pyelonephritis or vascular disease – probably, both were significant. And, although a fibrinous pericarditis provided anatomic evidence that some renal insufficiency was present, there appeared to be enough residual renal parenchyma to maintain function until heart failure supervened.

The brain weighed 985 gm. and showed evidence of mild general atrophy together with patches of severe atheroma in the arteries at the base. The most conspicuous external lesion was a depression, 3 cm. in diameter, on the lateral surface of the right cerebrum at the junction of the inferior parietal lobule and the occipital lobe. Coronal sections confirmed this to be an area of old infarction in-

Photomicrograph of a section at the level of the thalami showing the normal size of the subthalamic nuclei. The identifying notch was cut on the right side. (Klüver stain, × 4)

volving the posterior part of the right superior temporal gyrus and adjacent inferior parietal lobule and occipital lobe with involvement of white matter as well as gray so that, at the vestibule, the surface and the ependyma were in close proximity. These sections showed also a small area of necrosis of the cortex in the depth of a sulcus in the inferior part of the right frontal lobe and a few pits of perivascular atrophy beneath both lenticular nuclei. We paid, of course, particular attention to the subthalamic nuclei, and the only suggestion of a lesion to the naked eye was a slight gray discoloration in the anterior part of the right nucleus about a congested vessel leading from the internal capsule. Microscopic examination of the nuclei showed, however, no difference on the two sides (see illustration), so I think the slight gray discoloration was a fixation artefact. Hyaline arteriosclerosis of small vessels in this region was conspicuous as it was on the opposite side and in several other regions. There was perhaps a slight loss of neurons in the nuclei and rather more lipofuscin pigment in the cytoplasm of the residual neurons than one would expect at 53 years but, again, no difference on the two sides. Microscopic examination of the large infarct and the small area of necrosis showed the usual picture of glial scars. Evidence of large vessel occlusion was lacking in our sections.

So it appears to me that we have a case of hemiballismus occurring thirteen years ago with recovery. The evidence points to an infarct in the right cerebrum as the responsible lesion. It is true that our microscopic preparations of the lenticular nuclei are not very extensive but those available do not show anything beyond perivascular atrophy, and, at the gross examination, we had a careful look for any suspicious areas in view of the interest of the case. We can be certain that, at the time this infarct developed, the area of circulatory disturbance was much greater than the area of shrunken scar at necropsy. Whether the congestion or edema around the area of necrosis at that time extended to involve the subthalamic nucleus temporarily or to interrupt some as yet unknown circuit between parietal lobe, basal ganglia, and subthalamic nucleus can only be a subject for speculation. I think that it is useful for us to consider even perhaps as unique a case as this in view of the current interest in the pathology of involuntary movement and the growing appreciation that cases of hemiballismus recover for a time.[1] A case of hemiballismus associated with a parietal lesion was reported by Kinnier Wilson in 1929.[2]

I cannot explain with certainty the etiology of this old infarct. The three possibilities appear to be embolism, large artery disease, and small artery thrombosis. Evidence for the first two is not convincing. Although stigmata of rheumatic heart disease were present at autopsy, we had only a suggestion of peripheral embolism in another organ (the left kidney) and no one recorded an episode of fibrillation during the numerous examinations in 1943. For these reasons, I think cerebral embolism unlikely. The internal carotid arteries were not dissected in the neck at autopsy, and, therefore, I cannot exclude this possibility of occlusion of the right one as a cause of the infarct in 1943. I think it is unlikely in view of the age of onset and the duration of subsequent disease. So, by indefinite exclusion, I find myself in agreement with Dr. Biehl and go for arteriosclerosis with or without thrombosis in a branch of the right middle cerebral artery as the cause of the infarct.

Clinical Diagnosis

Old infarction in right subthalamic nucleus and in right posterior parietal region (air study). Hypertensive cardiovascular disease. Arteriolar nephrosclerosis. Uremia.

Dr. Biehl's Diagnosis

Multiple infarctions in the cerebrum; old infarction in the right basal ganglia on the basis of atherosclerosis. Generalized cerebral atrophy, atherosclerotic. Pyelonephritis. Hypertensive cardiovascular disease. Uremia.

Pathologic Diagnoses

Old infarct of right cerebrum involving right inferior parietal lobule, adjacent occipital lobe, and temporal lobe. Arteriosclerosis of cerebral arteries. Slight general cerebral atrophy. Cardiovascular hypertrophy. Chronic rheumatic valvulitis with minimal mitral disease. Hypertension. Generalized arteriosclerosis. Old infarct of left kidney. Chronic pyelonephritis. Arteriole and arteriolar nephrosclerosis. Acute erosive gastritis. Chronic passive congestion of liver. Ascites. Lobular pneumonia. Pulmonary edema and congestion. Bilateral pleural effusion.

DR. BIEHL: Could the old clot in the kidney be a result of local inflammation?

DR. SMITH: Yes, it could. It is, I think, unlikely because evidence of inflammation in the surrounding tissue is inconspicuous.

DR. OSHER: Was there any other lesion in the brain other than the major lesion?

DR. SMITH: There was a small area of shrinkage in the depths of a fissure in the inferior part of the right frontal lobe at the level of the caudate nucleus and a few pits of perivascular atrophy around the small vessels in the lenticular nuclei; but no other significant lesions.

DR. BIEHL: What about the other kidney? Was it involved by pyelonephritis too?

DR. SMITH: Yes.

DR. BIEHL: But it wasn't particularly shrunken?

DR. SMITH: No; the one was shrunken to 65 gm.

DR. BIEHL: You point out the role of heart failure in her death, but heart failure is common in the syndrome of uremia. What with the progressive symptoms, the gastrointestinal hemorrhage, and the blood urea nitrogen, which is not high enough for the fatal uremic syndrome, we can't measure the severity of uremia by the level of blood urea nitrogen. It would seem that death was due to uremia with accompanying heart failure. But were these kidneys diseased enough to produce uremia?

DR. SMITH: The kidneys were certainly diseased enough to cause significant impairment of renal function. There was a fair amount of residual renal tissue, I would say, and the presence of the large pleural effusions, the considerable ascites, congested liver, and pulmonary edema all indicate to me heart failure. Maybe I look on uremia in a somewhat different way from you, but I would point out a heart failure component decidedly in this case.

Are the signs described in 1943 usual with a parietal lesion? In summary they were: pronator sign of the outstretched left upper extremity, reduced tonus in the left extremities, hyperactive deep reflexes, constant dorsiflexion of left great toe, and gentle plantar stimulation eliciting nothing but movement of the whole limb with a deeper stimulus.

DR. ARING: I would say they are compatible with a parietal lesion.

DR. BIEHL: What about the decrease in muscle tonus with exaggeration of deep reflexes; is this compatible with effects of hemiballismus?

DR. ARING: When I recorded these signs, undoubtedly I was intent upon the luysian nucleus as the localization. We see these hand and arm signs in chorea particularly. Tonus is reduced in lesions in the lower basal ganglia. However, reduction in tonus with increased deep reflexes may occur with lesions of the parietal lobe. We have seen patients with profound loss of sensation due to central lesions move their affected extremities about in the most bizarre manner. In some cases, the phenomenon resembles the voluntary movements utilized by people with a numb and tingling extremity – in constant motion in an attempt to dispel the strange feeling. In others, the movements are like those associated with extrapyramidal disease. One such patient was sent to me for an opinion as to whether or not pallidotomy was advisable! Of course, these latter cases have a classical parietal lobe syndrome with astereognosis and the rest of the higher sensory deficit, which was not demonstrated in the case discussed here today.

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Neurology

BOOK REVIEWS

A Primer of Cerebral Palsy

Joseph D. Russ and Hyman R. Soboloff, 77 pp., ill., Charles C Thomas, Springfield, Ill., 1958. $4

The aim of this brief monograph from the American Lecture Series is to present the many aspects of cerebral palsy.

The importance of the team approach to the problem is stressed. A realistic program accepted by both the team and parents is essential if unfortunate children with cerebral palsy are to be helped to their greatest potential. The monograph deals mostly with basic principles and provides an excellent starting point for anyone interested in cerebral palsy.

J.P.R.

Viral Encephalitis

William S. Fields and Russell L. Blattner, 225 pp., ill., Charles C Thomas, Springfield, Ill., 1958. $7

This book contains a series of papers which were presented as a symposium at the Fifth Annual Scientific Meeting of the Houston, Texas, Neurological Society.

Although the individual sections are well written and informative, the book has certain omissions, a lack of balance, and failure of continuity. For example, the chapter on pathology is placed near the end of the volume and is much longer than the other chapters. In the first chapter, a classification of viral encephalitis is amplified by a more detailed classification of arthropod-borne encephalitis.

The second chapter details the characteristics of arthropod-borne encephalitis and is followed by a chapter on the diagnosis of virus encephalitis. The chapter on postencephalitic manifestations emphasizes the absence of progressive sequellae in western equine encephalitis and the occurrence of greater sequellae among younger patients. The chapter on pathology deals with those virus infections characterized by nuclear inclusions. Current trends in the control of viral encephalitis are discussed in the final chapter.

J.R.B.

Clinical Neuroanatomy, Neurophysiology and Neurology: Atlas III

by Louis Hausman, 522 pp., Charles C Thomas, Springfield, Ill., 1958. $9.75

This is the third volume of a series presenting the complete anatomy of the nervous system correlated with its applied physiology.

The book is integrated with Atlas I which presents sections of the spinal cord, brain stem, and forebrain and with Atlas II which describes consecutive stages of the reconstruction of a model of the nervous system.

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This book is of vital importance to the whole field of medicine because it brings together knowledge of the subject now available from the entire world. It embraces scientific disciplines related to research on the organic approach to mental illness and presents a broad span of different points-of-view of scientists from many countries whose reports represent years and years of investigation and experience.

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(Continued on page 22A)

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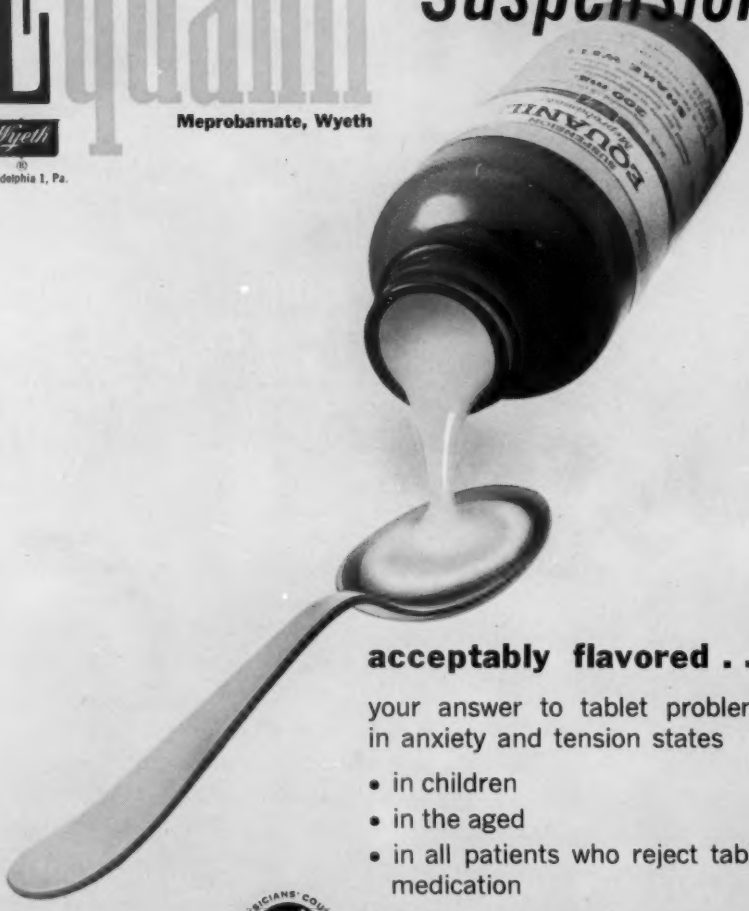

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PRODUCTS AND SERVICES

(Continued from page 18A)

EPILEPSY IN THE UNITED STATES

According to the current issue of *Patterns of Disease* published by Parke, Davis & Company for the medical profession, at least 1 in every 200 Americans has epilepsy. The disease is as common as diabetes or active tuberculosis and occurs 4 times more often than poliomyelitis.

Estimates of number of persons with epilepsy range from 640,000 to 1,700,000, but no precise estimate can be made. Approximately 52,000 people have their first attack each year. Incidence of epilepsy is 20% higher in men.

In most patients, causes of epilepsy are unknown. However, approximately 3 out of 10 epileptic patients have evidence of brain lesion. In one study of 535 patients who had organic brain lesion prior to their first seizure, 4 leading causes of seizure were: injury at birth, injury after birth, exposure to infections, and prenatal conditions.

Among the disturbances leading to epileptic seizures, says *Patterns*, are injections of convulsant drugs, photic stimulation, alcoholic excess, and hypoglycemia.

With the use of anticonvulsants and other drugs, 80 to 90% of epileptics can enjoy complete or partial freedom from seizures and can expect to lead normal lives. Control of seizures can be achieved in most patients through the careful administration of anticonvulsant drugs singly or in combination, *Patterns* says.

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FEBRUARY 1959

American Board Examinations Scheduled for 1959 The American Board of Psychiatry and Neurology announces three examinations in 1959. The first, in New Orleans (March 16 and 17); the second, in Chicago (October 19 and 20); the third, in New York City (December 14 and 15)....Inquiries should be addressed to Dr. David A. Boyd, Jr., Secretary-Treasurer American Board of Psychiatry and Neurology, Inc., 102-110 Second Avenue, S. W., Rochester, Minn.

New Officers of Argentine League Against Epilepsy Doctor Alberto Delmar of the Faculty of Medicine, Buenos Aires, announces that the newly elected officers of the Argentine League Against Epilepsy are: Dr. Hector J. Vazquez, President, Dr. Bernabe Cantlon, Vice-President, Dr. Ana Catz, Secretary, Dr. Alberto Delmar, Assistant Secretary, and Dr. Jose Benaim, Treasurer. The new officers were elected at the meeting of the active members, held in Buenos Aires, December 16, 1958.

New Training Programs Inaugurated in Basic Neurological Sciences Two new graduate training programs in basic neurology have been organized with the support of grants from the National Institute of Neurological Diseases and Blindness ....The first is a training program in the biochemical aspects of neuropharmacology under the direction of Oliver H. Lowry of Washington University in St. Louis. This program has been formulated primarily to aid doctors of medicine who wish to do research on the nervous system. It is closely integrated with a new training program in neurophysiology as well as with other departments with related interests at Washington University. Inquiries or applications for postdoctoral traineeships under this program should be sent to Prof. Oliver H. Lowry, Washington University School of Medicine, St. Louis 10....The second new graduate training program is in neuroanatomy and has been organized at Columbia's College of Physicians and Surgeons by Malcolm B. Carpenter. This program, also supported by the NINDB, is operated in conjunction with similar programs in basic neurology at the New York Neurological Institute; H. Houston Merritt is Director of the Neurology Service. This program includes training in histochemistry of neural tissue, degeneration and regeneration of neural tissue, developmental and comparative neurology, experimental neurology, stereotaxic methods and their application, histogenesis of neural tissue, tissue

culture studies, and electron microscopic structure of sensory receptors in neural tissue, and muscle. Eligible candidates for fellowships must have an M.D. or a Ph.D. degree. Fellowships will be awarded for a period of at least one year and are renewable.... For additional information write Malcolm B. Carpenter, M.D., Associate Professor, Department of Anatomy, Columbia University, College of Physicians and Surgeons, New York City 32.

Humphrey and Khrushchev Agree on International Neurological Research

According to a New York press release (December 2, 1958), Sen. Hubert Humphrey (D, Minn.) and Soviet Premier Nikita Khrushchev, during the former's recent visit to the USSR, disagreed on many things, but they did agree that "the world is hungry for some evidence of effective Soviet-American collaboration" and the best way to start is by cooperating in medical research. Highlighted by Sen. Humphrey was the need of international cooperation to conquer cancer, heart disease, and the killing and crippling neurologic disorders of early life arising from disease or injury in the perinatal period. The third-ranking Democratic member of the Senate Committee on Foreign Relations contined: "We must find out what biochemical and other changes occur in the pregnant mother and in the fetus that may result in or contribute to brain damage, cerebral palsy, epilepsy, mental retardation, speech and hearing disorders and the like in the newborn." Then Sen. Humphrey added, "Fortunately, the United States has launched an extensive campaign of perinatal study. Now I hope and expect that bilaterally and multilaterally (through WHO) Soviet gynecologists, obstetricians, pediatricians, neurologists and other specialists will join with ours in making their fullest contributions."....Sen. Humphrey went to Moscow principally as Chairman of a Government Operations Subcommittee to make a study of problems pertaining to international health, research, assistance, and rehabilitation. Besides interviewing Premier Khrushchev, he made a series of specific suggestions to Dr. V. M. Zdhanov, Deputy Minister of Health, and Professor Semyon Sarkisov, Vice-President of the Academy of Medical Sciences....The Senator was accompanied to Moscow by Mrs. Humphrey and by the Committee's Staff Director for the Medical Research Project, Mr. Julius N. Cahn.

Mental Retardation Group To Hold International Conference

The First International Conference on Mental Retardation will be held at the Eastland Hotel, Portland, Me. (July 27 through 31). The program and conference is being organized by the Maine chapter of the American Academy of Pediatrics, the Division of Maternal and Child Health, Maine Department of Health and Welfare, and the Pineland Hospital and Training School. The program will include, in its five days of general sessions, presentations on brain anatomy, the reticular system, head anomalies, phenylketonuria, lipoidosis, birth injury, embryology,

infectious mongolism, erythroblastosis, and behavior disorders. The conference is open to all physicians throughout the world.... Inquiries should be sent to Dr. Ella Langer, Chairman, Arrangements Committee, State of Maine Department of Health and Welfare, Augusta, Me.

Easter Seal Grant Awards Announced The Board of Trustees of the Easter Seal Research Foundation (William T. Sanger, Chairman), announces the award of six new research grants and five renewal grants in the amount of $108,510. These awards were made by the Board of Trustees at their meeting, September 29, 1958. Included in the actions was approval of a one-year grant for $15,000 to Doctors Russell Meyers and William J. Fry on ultrasonic neurosurgical therapy and rehabilitation and pathophysiology of cerebral palsied patients exhibiting choreoathetotic, hypertonic, and akinetic syndromes. The Trustees also recommended that the Easter Seal Foundation organize an institute on the design of experiments and rehabilitation to be held in conjunction with the Eighth World Congress of the International Society for the Welfare of Cripples to be held in New York City (1960) and being co-sponsored by the National Society for Crippled Children and Adults....Inquiries about the program of the Easter Seal Research Foundation should be sent to Dr. William Gellman, Director, Easter Seal Foundation, National Society for Crippled Children and Adults, 2023 W. Ogden Avenue, Chicago 12.

A Russian Neurologic Mission To Visit the United States A Soviet team of scientists will visit medical research centers in this country sometime in February. The Soviet group constitutes a return mission for an American NINDB sponsored mission, the first of its kind in the field of neurology, which recently visited the USSR (See December 1958 Newsletter). On the Soviet team are Profs. Anichkov, Anokhin, Chernigovsky, Rusinov, and Zakusov. The members of the U.S. mission who are now back in the United States were: Francis M. Forster, Chairman; N. C. Woolsey; Paul I. Yakovlev; Louis S. Goodman; Henry W. Woltman; and Karl Frank.

Reese Going to Japan Hans H. F. Reese, Professor of Neurology, School of Medicine of the University of Wisconsin, is to visit Tokyo and other places in Japan as a consultant to an NINDB project in geographic neuropathology in the Orient. This project is under the immediate supervision of Leonard T. Kurland, Chief, Epidemiology Branch, National Institute of Neurological Diseases and Blindness. It is part of a larger collaborative project centering on geomedical studies in amyotrophic lateral sclerosis, multiple sclerosis, and other neurologic disorders in Guam, Japan, and Alaska. Also included is a study on a type of toxic fish poisoning known in Japan as

Minamita disease....Prof. Reese, a former president of the American Neurological Association, has had a wide experience as a consultant to research projects abroad. He has served as a consultant to the Office of Scientific Research Development, Washington, D.C.; as a combat scientist (ETO) from 1944 to 1945 and as a medical adviser, and in the U.S. bombing survey (ETO-Air Corps), in 1945.

Briefs Roger Rossiter, Professor and Head of the Department of Biochemistry, University of Western Ontario (Faculty of Medicine), a member of the NINDB Board of Scientific Counselors, is off on a visiting professorship in biochemistry, Australian National University, Canberra, Australia....Charles M. Poser has been promoted to Assistant Professor of Medicine and head of a newly created Section of Experimental Neurology at the University of Kansas Medical Center. This section has added a Laboratory of Neurochemistry under Dr. Lewis C. Mokrasch. Dr. Poser also is now directing the training program in clinical neurology replacing Dr. A. Theodore Steegmann who remains as Professor of Neurology.... The joint meeting of the Philadelphia Neurological Society and the Section of Neurology, Neurosurgery, and Psychiatry of the Medical Society of the District of Columbia was held at the Barclay Hotel in Philadelphia on November 7, 1958....Sad news has been received of the death of Ernest Sachs (December 2, 1958), one of the neurosurgical pioneers in the United States; and, Professor Jarbas Pernambucano de Melo (July 4, 1958), neurologist in the faculty of the University of Recife, Brazil, at the untimely age of 39 years.

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References: 1. Barsa, J. A.: Am. J. Psychiat. 115:79, July 1958. 2. Graffagnino, P. N., Friel, P. B. and Zeller, W. W.: Connecticut M. J. 21:1047, Dec. 1957. 3. Hollister, L. E., Elkins, H., Hiler, E. G. and St. Pierre, R.: Ann. New York Acad. Sc. 67:789, May 9, 1957. 4. Pennington, V. M.: Am. J. Psychiat. 114:257, Sept. 1957. 5. Tucker, K. and Wilensky, H.: Am. J. Psychiat. 113:698, Feb. 1957.

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Zier, A. and Doshay, L. J.: Procyclidine Hydrochloride (Kemadrin) Treatment of Parkinsonism in 108 Patients, Neurology (July) 1957.

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Lerner, P. F.: Kemadrin, a New Drug for Treatment of Parkinsonian Disease, J. Nerv. & Ment Dis. 123:79 (Jan.) 1956.

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